GL14 Continued

Thirty-eight healthy volunteers who cycled parallel to a major traffic corridor for 20 min (mean UFP concentration 2.9×10^4 particles cm^{-3}) experienced a minor increase in blood inflammatory cell distribution compared to cycling in a clean air environment, although the role of UFPs as distinct from $PM_{2.5}$ was not clear (Jacobs et al., 2010). UFP and EC exposure in 12 healthy non-smoking individuals cycling in traffic (mean UFP concentration 2.8 to 4.1×10^4 particles cm^{-3}) for 1 h was weakly associated with acute effects; decreased lung function and increased exhaled NO (as a marker of airway inflammation) were observed 6 h post-exposure (Strak et al., 2010). Oxidative DNA damage observed in 15 healthy subjects was positively correlated with cumulative UFP exposure, to which 1.5 h of cycling during rush hours (mean UFP concentration 3.2×10^4 particles cm^3) contributed substantially and resulted in greater damage compared to indoor cycling on an ergometer (Vinzents et al., 2005). Concentrations of other pollutants (PM_{10}, NO_x, CO) measured at fixed-sites were not associated with oxidative DNA damage.

UFP exposure resulted in modest effects among 34 healthy subjects that commuted by automobile, bus or bicycle for 2 h (median UFP concentration 2.7 to 4.4×10^4 particles cm^{-3}); peak expiratory flow decreased slightly and airway resistance increased immediately following exposure, and a significant increase in exhaled NO was observed 6 h post-exposure for automobile and bus commuters, but not cyclists (Zuurbier et al., 2011).

As the respiratory minute ventilation of cyclists is 2–4.5 times that of automobile and bus passengers (Zuurbier et al., 2009; Int Panis et al., 2010), the potential dose of inhaled UFPs received during active transport may be significantly higher than that in non-active modes, and recent health effects studies have already begun to adopt a more dose-oriented approach to reflect this (Zuurbier et al., 2011).

8.2. Health-compromised individuals

8.2.1. Asthmatics

Asthma exacerbations can be triggered due to oxidative stress and inflammation caused by UFPs in the lungs of susceptible individuals (Weichenthal et al., 2007). Reductions in lung function and increased daily symptoms in asthmatics and COPD patients attributable to elevated UFP concentrations have been observed in epidemiologic studies, with more immediate effects seen first in the respiratory system, and a delayed response of cardiovascular effects (Wichmann and Peters, 2000; Ibald-Mulli et al., 2002).

Consistent asymptomatic reductions in lung function (FEV_1, FVC) and increases in both inflammatory biomarkers and airway acidification were observed in 60 persons with mild or moderate asthma who walked for 2 h along a busy London street affected by diesel exhaust (median UFP concentration 6.4×10^4 particles cm^{-3}) (McCreanor et al., 2007). The effects were more frequently associated with UFP and EC concentrations than those of $PM_{2.5}$ and NO_2. Significantly reduced respiratory effects were observed when subjects walked along a route less affected by traffic emissions (median UFP concentration 1.8×10^4 particles cm^{-3}).

Fourteen mild asthmatics exposed to road tunnel air (median UFP concentration 2.3×10^5 particles cm^{-3}) for 2 h while alternating between exercising on a bicycle ergometer and resting experienced no changes in bronchial responsiveness and most lung function parameters, although peak expiratory flow decreased, and minor indications of inflammation were measured in nasal lavages, but not blood samples (Larsson et al., 2010).

8.2.2. Diabetics

Exposure to pollutants (median UFP concentration 4.3×10^4 particles cm^{-3}) during 1.5–1.8 h automobile highway trips made by 21 type 2 diabetics was shown to elicit a decrease in high-frequency heart rate variability the day after exposure, which was more associated with the interquartile range of UFP concentration compared to those of $PM_{2.5}$, NO_2 and CO, albeit not significantly (Laumbach et al., 2010). An increased low frequency to high frequency heart-rate variability ratio was observed immediately post-exposure that was not consistent with other observations, although confounding effects not present in the aforementioned finding may have influenced this result.

8.2.3. Elderly persons

Nineteen elderly subjects that were exposed to unfiltered and filtered air during 2 h automobile trips on Los Angeles freeways (mean unfiltered UFP concentration 0.78 to 1.1×10^5 particles cm^{-3}) experienced a 20% decrease in the incidence of atrial ectopic heartbeats and 30% decrease in cardiopulmonary stress biomarkers under the filtered compared to the unfiltered condition (Cascio et al., 2009; Hinds, 2010). Other measured parameters (lung function, indicators of inflammation, blood pressure) did not vary significantly between the two conditions. The observed atrial arrhythmia was ascribed to increased intra-atrial pressure, and was associated with UFP concentrations rather than gases or particle mass (Cascio et al., 2009; Hinds et al., 2010). The significance of such events is related to their role in causing more sustained arrhythmias.

8.3. Summary

Commute-time exposure to traffic and attendant pollutant emissions, noise and stress has been associated with increased risk of serious adverse health effects such as myocardial infarction (Peters et al., 2004). The specific role of UFPs as a causative agent of such effects is not clear, and the findings of the limited number of health effects studies addressing commuter exposure to vehicle emissions are mixed. However, some initial trends are emerging. While it is inherently difficult to separate the effects of UFPs from those other pollutants within the real-world exposure scenarios employed by the studies described above, the observed health effects were generally associated most strongly with UFP concentrations. Furthermore, the use of filtered air exposure scenarios in the Los Angeles freeway study (Cascio et al., 2009; Hinds, 2010) reduced particle concentration by >95% compared to the unfiltered condition but did not affect the level of gaseous pollutants, yet there was a marked difference in the cardiac effects observed between the two scenarios. The effects observed by McCreanor et al. (2007) were greater in those with moderate compared to mild asthma, and the degree to which this is true of other susceptible groups (i.e. increasing effects with increasing disease severity) is unclear. The 10 commuter health effects studies performed to-date have yielded valuable information; however, it is clear that further studies are required in order to better elucidate the role of UFPs.

9. Modelling exposure

9.1. Approaches employed to-date

The ability to accurately model in-transit UFP exposure concentrations has numerous attractive applications in urban planning, transport and policy development. The majority of published studies that developed models employed a multivariate regression approach that incorporated meteorologic, traffic or other pollutants as independent variables (Krause and Mardaljevic, 2005; Vinzents et al., 2005; Weichenthal et al., 2008; Boogaard et al., 2009; Kaur and Nieuwenhuijsen, 2009). Given

GL14 Continued

the potential for variability in the strength of associations between the independent variables and measured UFP concentrations discussed in sections 5, the external validity of these models is unknown. However, the models were of the explanatory type, and were developed in order to assess the effect of various parameters on UFP concentration measured in a specific location. Their ability to predict exposure concentrations varied from fair ($R^2 = 0.35$) to very good ($R^2 = 0.74$). The influence of mode-dependent parameters like ventilation were either included in a qualitative sense (e.g. ventilation setting or window position) or not included at all. This limitation was raised by both Briggs et al. (2008) and Weichenthal et al. (2008).

Several recent studies (Fui et al., 2008; Xu and Zhu, 2009; Knibbs et al., 2010) have sought to overcome the limitations described above by adopting a more mechanistic, mass-balance modelling approach for automobiles. This has been based on measurements of the effects of cabin ventilation, filtration, particle penetration or deposition on in-cabin concentrations (Qi et al., 2008; Gong et al., 2009; Knibbs et al., 2009a; Xu et al., 2010). These studies have generally shown very good results when validated with experimental data. The main limitation of such approaches is that they require the input of an initial on-road or in-cabin UFP concentration. Therefore, there is a clear need to couple models capable of predicting outdoor or on-road concentrations with those focussed on predicting what proportion of these concentrations reach occupants, and how particle dynamics will affect concentrations through time. Moreover, further refinement of models for predicting exposure in active transport modes will be of significant utility. In summary, there is both substantial need and scope for development of models capable of accurate prediction of UFP exposure concentrations in-transit.

9.2. Spatial and temporal aspects of exposure

Efforts to improve understanding of the spatial and temporal nature of UFP exposures during transit have benefited greatly from the use of Global Positioning Systems (GPS) and Geographic Information Systems (GIS), usually at the measurement and analytical stages, respectively. Gulliver and Briggs (2005) described the development and use of a GIS-based model for predicting exposure to PM_{10} (particles < 10 μm) during transit, however, the application of spatial technologies to UFPs has to-date been limited to a handful of in-transit studies (Hvidberg, 2006; Thai et al., 2008; Berghmans et al., 2009; Boogaard et al., 2009; Pattinson, 2009; Int Panis et al., 2010). Synchronised video recordings have been included in some studies (Kaur et al. 2006; Berghmans et al., 2009), which affords an additional perspective from which analyses can be performed.

Given the good level of spatial data quality obtainable from even the more basic mobile telephones at present, the integration of such data into exposure studies will assist data interpretation and help to form a more complete and accurate assessment of pollutant exposure and dose for large study populations (Jerrett, 2010). The appropriateness and capability of mobile telephones to record spatial data and photographs during commuting has already been established by Pooley et al. (2010), and Pattinson (2009) collected such data in addition to UFP measurements when commuting by bicycle.

Land use regression (LUR) is an application of GIS that is gaining momentum as a tool with which to predict exposure to a variety of pollutants (see Hoek et al., 2008). The utility of LUR techniques to predict UFP concentrations and spatial variability is not well-established due to absence of extensive UFP monitoring networks; other (mainly gaseous) pollutants have been the focus of most work performed to-date. However, a recent study has reported reasonable performance of LUR when applied to UFP concentrations in Amsterdam, and comparable predictive utility was observed between the LUR model for UFPs and those for other pollutants (Hoek et al., 2011). LUR is an emerging technology that will increasingly find applications in prediction of personal exposure to a range of pollutants, albeit with an attendant need for validation based on measurements (Hoek et al., 2008). This highlights the need for high-quality databases of concomitant in-transit UFP and spatial measurements.

10. Further research needs

10.1. In-transit contribution to daily exposure

The significance of in-transit UFP exposure is highly dependent on personal, demographic and occupational context. UFP concentrations encountered on the commute to and from work will exert much greater influence on the total daily exposure of a non-smoking office worker than a smoker or someone who experiences high occupational exposure. Likewise, the health effects of the same exposure on an adult and child are likely to vary. Without better understanding of the characteristics of 24 h UFP exposure for numerous demographic groups, knowledge of in-transit exposure alone is of reduced utility. However, it is useful to be able to determine, for a given location, the transport mode in which highest concentrations occur and the factors that determine this. Such information has numerous valuable planning and policy applications.

A handful of studies have estimated the influence of measured in-automobile UFP concentrations on total exposure. Two were based on Los Angeles residents (Zhu et al., 2007; Fruin et al., 2008), and their estimates ranged from 10 to 50% and 33 to 45%, respectively. Wallace and Ott (2011) measured UFP concentrations in a wide range of microenvironments in two US cities and estimated the in-automobile contribution to total exposure to be 17%, which they attributed to the relatively low density of traffic and diesel trucks on the roadways they measured compared to LA. In all cases, the time spent in automobiles was assumed to be about 90 min per day. The applicability of the estimates reached by these studies to other regions is unknown, but they have established a range within which automobile commutes in urban areas may be expected to contribute to daily UFP exposure. These estimates have flagged this topic as one requiring further investigation, preferably including several transport modes.

It is important to consider the distinction between UFP concentration and exposure (Krause and Mardaljevic, 2005). A high concentration experienced for a brief duration can result in a lower exposure than a low concentration for a longer period. This underscores the need for both accurate time-activity pattern data across broad demographic groups and representative UFP measurements within the various microenvironments in which time is spent. Until more expansive UFP exposure studies that follow large groups of people of varying time-activity patterns are completed, the ability to discern the range of commute-time's specific contribution to total exposure is constrained.

10.2. High exposure professions

The magnitude of UFP exposures incurred by people whose occupation requires them to spend extended period in-transit is poorly understood. Professional drivers, bicycle couriers, police officers and other groups whose work day is constituted by long periods in transport microenvironments may all be at risk of substantially elevated exposure compared to the general population. Riediker et al. (2004) reported the negative health effects of

GL14 Continued

GL14 Continued

in-vehicle $PM_{2.5}$ exposure on young and healthy police officers during 9 h shifts in patrol cars. Similar studies focussed towards UFPs are required.

10.3. Exposure-health effects link

Various acute human health effects caused by UFP exposures have been investigated in controlled exposure studies using a range of subject groups. However, their relevance to in-transit exposures is unclear. There have been precious few studies that measured the effects of in-transit exposures on health end points, and these were described in section 8. There is a significant need for further studies in this area, as they will serve to bolster the link between exposure and health effects, and this will have implications across policy, planning and public health arenas (de Nazelle and Nieuwenhuijsen, 2010). Furthermore, given the substantial variability in minute ventilation between occupants of different modes (Zuurbier et al., 2009; Int Panis et al., 2010), the transition from an exposure to dose-oriented approach is likely to yield data of greater relevance to studies of health effects.

10.4. Data from the developing world

A striking feature of the English language literature we searched is the almost complete absence of studies performed in developing regions; with the exception of only the cycling study performed in Bogota, Columbia by Fanara (2003) and cited by Kaur et al. (2007), no other studies from developing countries were identified. This shortcoming is compounded by the generally poor air quality experienced in these regions (Han and Naeher, 2006) and their large populations and urban density. The effect of this combination of factors is that very high UFP exposures are likely to occur for large numbers of people, but the magnitude of such exposures is unknown. Studies of commuter exposure to particulate mass (RSP, PM_{10}) performed in Delhi and Hanoi have reported exceptionally high concentrations (Saksena et al., 2007, 2008). Moreover, in addition to walking, the most popular modes of transport, such as bicycles, scooters, motorcycles and 3-wheelers (tuk-tuks, auto-rickshaw etc), are unlikely to afford significant protection from the emissions of proximate traffic, which can include a substantial proportion of high emitting two-stroke vehicles. There is a clear need to redress the scarcity of research in this area.

10.5. Other needs

Major needs in future in-transit UFP exposure studies have been outlined above, and numerous other aspects requiring additional research have been suggested throughout this review. Further investigation of the variability inherent in the determinants of exposure discussed in section 5 is required to permit better appreciation of their effects. There is also an obvious need for improved modelling techniques, incorporating GIS, and for further comprehensive assessments of the health risk-benefit balance for active transport modes (de Nazelle et al., 2009; de Hartog et al., 2010).

11. Conclusions

In our analysis of 47 studies comprising approximately 3000 trips undertaken in 6 transport modes, we found that highest trip-weighted mean concentration occurred in automobile cabins during tunnel travel (3.0×10^5 particles cm^{-3}), and the lowest whilst cycling (3.4×10^4 particles cm^{-3}). Mean concentrations in bus, automobile (non-tunnel travel), rail, and walk modes were generally comparable. However, UFP exposure (and dose) during time spent in-transit is strongly dependent on a range of mode-specific and more general determinants, including, but not limited to, the effects of: meteorology, traffic parameters, cabin ventilation, filtration, deposition, UFP penetration, fuel type, exhaust treatment technologies, respiratory minute ventilation, route and microscale phenomena. Therefore, direct comparison of concentrations measured in different modes highlights general trends, but should not be extrapolated without detailed consideration of the above factors. Characterising the variability in the effects of these determinants will be an important aspect of future work.

There is preliminary evidence to suggest that time spent in-transit can contribute substantially to total daily exposure, and future studies require comprehensive assessment of 24 h UFP exposures across a broad demographic spectrum. Moreover, the range and variability of acute health effect associated with in-transit exposures are not well understood, and further studies are required to supplement the findings of the limited number performed to-date.

Transport is a ubiquitous component of life, and initial evidence suggests that UFP exposures incurred during this time can contribute substantially to daily exposure and be associated with adverse health effects in susceptible and healthy persons. Further research to better define this link is therefore well-justified, and will be of considerable benefit to urban planning, policy development and public health.

Acknowledgements

We thank Dr. Colin Solomon for his interest in this work and the useful feedback he provided.

Appendix. Supplementary information

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.atmosenv.2011.02.065.

References

Aarnio, P., Yli-Tuomi, T., Kousa, A., Mäkelä, T., Hirsikko, A., Hämeri, K., Räisänen, M., Hillamo, R., Koskentalo, T., Jantunen, M., 2005. The concentrations and composition of and exposure to fine particles (PM2.5) in the Helsinki subway system. Atmospheric Environment 39, 5059–5066.
Araujo, J., Nel, A., 2009. Particulate matter and atherosclerosis: role of particle size, composition and oxidative stress. Particle and Fibre Toxicology 6, 24.
Ashmore, M.R., Dimitroulopoulou, C., 2009. Personal exposure of children to air pollution. Atmospheric Environment 43, 128–141.
Asmi, E., Antola, M., Yli-Tuomi, T., Jantunen, M., Aarnio, P., Mäkelä, T., Hillamo, R., Hämeri, K., 2009. Driver and passenger exposure to aerosol particles in buses and trams in Helsinki, Finland. Science of the Total Environment 407, 2860–2867.
Badland, H.M., Duncan, M.J., 2009. Perceptions of air pollution during the work-related commute by adults in Queensland, Australia. Atmospheric Environment 43, 5791–5795.
Behrentz, E., Fitz, D.R., Pankratz, D.V., Sabin, L.D., Colome, S.D., Fruin, S.A., Winer, A.M., 2004. Measuring self-pollution in school buses using a tracer gas technique. Atmospheric Environment 38, 3735–3746.
Berghmans, P., Bleux, N., Panis, L.I., Mishra, V.K., Torfs, R., Van Poppel, M., 2009. Exposure assessment of a cyclist to PM10 and ultrafine particles. Science of the Total Environment 407, 1286–1298.
Bland, J.M., Kerry, S.M., 1998. Weighted comparison of means. BMJ 316, 129.
Boogaard, H., Borgman, F., Kamminga, J., Hoek, G., 2009. Exposure to ultrafine and fine particles and noise during cycling and driving in 11 Dutch cities. Atmospheric Environment 43, 4234–4242.
Briggs, D.J., de Hoogh, K., Morris, C., Gulliver, J., 2008. Effects of travel mode on exposures to particulate air pollution. Environment International 34, 12–22.
Brook, R.D., Rajagopalan, S., Pope III, C.A., Brook, J.R., Bhatnagar, A., Diez-Roux, A.V., Holguin, F., Hong, Y., Luepker, R.V., Mittleman, M.A., Peters, A., Siscovick, D., Smith Jr., S.C., Whitsel, L., Kaufman, J.D., 2010. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. Circulation 121, 2331–2378.
Brugge, D., Durant, J., Rioux, C., 2007. Near-highway pollutants in motor vehicle exhaust: a review of epidemiologic evidence of cardiac and pulmonary health risks. Environmental Health 6, 23.

Burtscher, H., Loretz, S., Keller, A., Mayer, A., Kasper, M., Artley, R.J., Strasser, R., Czerwinski, J. 2008. Nanoparticle filtration for vehicle cabins. SAE Paper 2008-01-0827.
Cascio, W.E., Katwa, L.C., Linn, W.S., Stram, D.O., Zhu, Y., Cascio, J.L., Hinds, W.C., 2009. Effects of vehicle exhaust in aged adults riding on Los Angeles Freeways. American Journal of Respiratory and Critical Care Medicine 179, A1175.
Cattaneo, A., Garramone, G., Taronna, M., Peruzzo, C., Cavallo, D.M., 2009. Personal exposure to airborne ultrafine particles in the urban area of Milan. Journal of Physics: Conference Series 151, 012039.
Cheng, Y.H., Liu, C.C., Lin, Y.L., 2009. Levels of ultrafine particles in the Taipei rapid transit system. Transportation Research Part D: Transport and Environment 14, 479–486.
Cortese, A.D., Spengler, J.D., 1976. Ability of fixed monitoring stations to represent personal carbon monoxide exposure. Journal of the Air Pollution Control Association 26, 1144–1150.
de Hartog, J.J., Boogaard, H., Nijland, H., Hoek, G., 2010. Do the health benefits of cycling outweigh the risks? Environmental Health Perspectives 118, 1109–1116.
de Nazelle, A., Nieuwenhuijsen, M., 2010. Integrated health impact assessment of cycling. Occupational and Environmental Medicine 67, 76–77.
de Nazelle, A., Rodriguez, D.A., Crawford-Brown, D., 2009. The built environment and health: impacts of pedestrian-friendly designs on air pollution exposure. Science of the Total Environment 407, 2525–2535.
Daigle, C.C., Chalupa, D.C., Gibb, F.R., Morrow, P.E., Oberdörster, G., Utell, M.J., Frampton, M.W., 2003. Ultrafine particle deposition in humans during rest and exercise. Inhalation Toxicology 15, 539–552.
Delfino, R.J., Sioutas, C., Malik, S., 2005. Potential role of ultrafine particles in associations between airborne particle mass and cardiovascular health. Environmental Health Perspectives 113, 934–946.
El-Fadel, M., Abi-Esber, L., 2009. In-vehicle exposure to carbon monoxide emissions from vehicular exhaust: a critical review. Critical Reviews in Environmental Science and Technology 39, 585–621.
Elder, A., Gelein, R., Silva, V., Feikert, T., Opanashuk, L., Carter, J., Potter, R., Maynard, A., Ito, Y., Finkelstein, J., Oberdörster, G., 2006. Translocation of inhaled ultrafine manganese oxide particles to the central nervous system. Environmental Health Perspectives 114, 1172–1178.
Fanara, M., 2003 (cited in Kaur et al., 2007). Personal exposure of ultrafine particles among cyclists in Bogota, Colombia. Paper presented at the 13th Annual Conference International Society of Exposure Analysis, Stresa, Italy.
Flachsbart, P.G., 2007. Exposure to carbon monoxide. In: Ott, Steinemann, Wallace (Eds.), Exposure Analysis. CRC Press, Boca Raton, pp. 113–146.
Frampton, M.W., 2007. Does inhalation of ultrafine particles cause pulmonary vascular effects in Humans? Inhalation Toxicology 19, 75–79.
Fruin, S., Westerdahl, D., Sax, T., Sioutas, C., Fine, P.M., 2008. Measurements and predictors of on-road ultrafine particle concentrations and associated pollutants in Los Angeles. Atmospheric Environment 42, 207–219.
Gauderman, W.J., Avol, E., Gilliland, F., Vora, H., Thomas, D., Berhane, K., McConnell, R., Kuenzli, N., Lurmann, F., Rappaport, E., Margolis, H., Bates, D., Peters, J., 2004. The effect of air pollution on lung development from 10 to 18 years of age. The New England Journal of Medicine 351, 1057–1067.
Geiser, M., Rothen-Rutishauser, B., Kapp, N., Schurch, S., Kreyling, W., Schulz, H., Semmler, M., Hof, V.I., Heyder, J., Gehr, P., 2005. Ultrafine particles cross cellular membranes by nonphagocytic mechanisms in lungs and in cultured cells. Environmental Health Perspectives 113, 1555–1560.
Gong, L., Xu, B., Zhu, Y., 2009. Ultrafine particles deposition inside passenger vehicles. Aerosol Science and Technology 43, 544–553.
Gulliver, J., Briggs, D.J., 2005. Time-space modeling of journey-time exposure to traffic-related air pollution using GIS. Environmental Research 97, 10–25.
Haagen-Smit, A.J., 1966. Carbon monoxide levels in city driving. Archives of Environmental Health 12, 548–551.
Hammond, D., Jones, S., Lalor, M., 2007. In-vehicle measurement of ultrafine particles on compressed natural gas, conventional diesel, and oxidation-catalyst diesel heavy-duty transit buses. Environmental Monitoring and Assessment 125, 239–246.
Han, X., Naeher, L.P., 2006. A review of traffic-related air pollution exposure assessment studies in the developing world. Environment International 32, 106–120.
Hertel, O., Hvidberg, M., Ketzel, M., Storm, L., Stausgaard, L., 2008. A proper choice of route significantly reduces air pollution exposure – a study on bicycle and bus trips on urban streets. Science of the Total Environment 389, 58–70.
Hill, L.B., Zimmerman, N.J., Gooch, J., 2005. A multi-city investigation of the effectiveness of retrofit emissions controls in reducing exposures to particulate matter in school buses. Clean Air Task Force report. Available online: http://www.catf.us/resources/publications/files/CATF-Purdue_Multi_City_Bus_Study.pdf (accessed 11.12.10).
Hill, L.B., Gooch, J., 2007. A multi-city investigation of exposure to diesel exhaust in multiple commuting modes. Clean Air Task Force report. Available online: http://www.catf.us/resources/publications/files/Multi_City_Commuter_Exposure_Report.pdf (accessed 11.12.10).
Hinds, W.C., 2010. Cardiovascular health effects of fine and ultrafine particles during freeway travel. Report prepared for the California Air Resources Board and EPA. Available online: http://www.arb.ca.gov/research/apr/past/04-324.pdf (accessed 21.02.11).
Hoek, G., Beelen, R., de Hoogh, K., Vienneau, D., Gulliver, J., Fischer, P., Briggs, D., 2008. A review of land-use regression models to assess spatial variation of outdoor air pollution. Atmospheric Environment 42, 7561–7578.
Hoek, G., Beelen, R., Kos, G., Dijkema, M., van der Zee, S., Fischer, P.H., Brunekreef, B., 2011. Land use regression model for ultrafine particles in Amsterdam. Environmental Science & Technology 45, 622–628.
Hoek, G., Boogaard, H., Knol, A., de Hartog, J., Slottje, P., Ayres, J.G., Borm, P., Brunekreef, B., Donaldson, K., Forastiere, F., Holgate, S., Kreyling, W.G., Nemery, B., Pekkanen, J., Stone, V., Wichmann, H.E., van der Sluijs, J., 2010. Concentration response functions for ultrafine particles and all-cause mortality and hospital admissions: results of a european expert panel elicitation. Environmental Science & Technology 44, 476–482.
Hvidberg, M., 2006. Tracking human exposure to ultrafine particles in Copenhagen using GPS. Epidemiology 17, S38.
Ibald-Mulli, A., Wichmann, H.E., Kreyling, W., Peters, A., 2002. Epidemiological evidence on health effects of ultrafine particles. Journal of Aerosol Medicine 15, 189–201.
Int Panis, L., de Geus, B., Vandenbulcke, G., Willems, H., Degraeuwe, B., Bleux, N., Mishra, V., Thomas, I., Meeusen, R., 2010. Exposure to particulate matter in traffic: a comparison of cyclists and car passengers. Atmospheric Environment 44, 2263–2270.
Jacobs, L., Nawrot, T.S., de Geus, B., Meeusen, R., Degraeuwe, B., Bernard, A., Sughis, M., Nemery, B., Int Panis, L., 2010. Subclinical responses in healthy cyclists briefly exposed to traffic-related air pollution: an intervention study. Environmental Health 9, 64.
Jacobson, M.Z., 2002. Atmospheric Pollution: History, Science and Regulation. Cambridge University Press, Cambridge, 399 p.
Jerrett, M., 2010. Toward a time-geography of exposure: novel technologies and emerging trends. Available online:. In: "Air Pollution and Health: Bridging the Gap from Sources to Health Outcomes" Paper 165Q3.4 http://aaar.2010specialty.org/pdfs/Abstracts_by_Science_Question.pdf (accessed 12.12.10).
Kaminsky, J.A., Gaskin, E.A.L.M., Matsuda, M., Miguel, A.H., 2009. In-cabin commuter exposure to ultrafine particles on commuter roads in and around Hong Kong's Tseung Kwan O Tunnel. Aerosol and Air Quality Research 9, 353–357.
Kaur, S., Nieuwenhuijsen, M.J., Colvile, R.N., 2005a. Pedestrian exposure to air pollution along a major road in Central London, UK. Atmospheric Environment 39, 7307–7320.
Kaur, S., Nieuwenhuijsen, M., Colvile, R., 2005b. Personal exposure of street canyon intersection users to PM2.5, ultrafine particle counts and carbon monoxide in Central London, UK. Atmospheric Environment 39, 3629–3641.
Kaur, S., Clark, R.D.R., Walsh, P.T., Arnold, S.J., Colvile, R.N., Nieuwenhuijsen, M.J., 2006. Exposure visualisation of ultrafine particle counts in a transport microenvironment. Atmospheric Environment 40, 386–398.
Kaur, S., Nieuwenhuijsen, M.J., Colvile, R.N., 2007. Fine particulate matter and carbon monoxide exposure concentrations in urban street transport microenvironments. Atmospheric Environment 41, 4781–4810.
Kaur, S., Nieuwenhuijsen, M.J., 2009. Determinants of personal exposure to PM2.5, ultrafine particle counts, and CO in a transport microenvironment. Environmental Science & Technology 43, 4737–4743.
Kettunen, J., Lanki, T., Tiittanen, P., Aalto, P.P., Koskentalo, T., Kulmala, M., Salomaa, V., Pekkanen, J. 2007. Associations of fine and ultrafine particulate air pollution with stroke mortality in an area of low air pollution levels. Stroke 38, 918–922.
Kittelson, D.B., 1998. Engines and nanoparticles: a review. Journal of Aerosol Science 29, 575–588.
Klepeis, N.E., Nelson, W.C., Ott, W.R., Robinson, J.P., Tsang, A.M., Switzer, P., Behar, J.V., Hern, S.C., Engelmann, W.H., 2001. The National Human Activity Pattern Survey (NHAPS): a resource for assessing exposure to environmental pollutants. Journal of Exposure Analysis and Environmental Epidemiology 11, 231–252.
Knibbs, L.D., de Dear, R.J., Atkinson, S.E., 2009a. Field study of air change and flow rate in six automobiles. Indoor Air 19, 303–313.
Knibbs, L.D., de Dear, R.J., Morawska, L., Mengersen, K.L., 2009b. On-road ultrafine particle concentration in the M5 East road tunnel, Sydney, Australia. Atmospheric Environment 43, 3510–3519.
Knibbs, L.D., de Dear, R.J., Morawska, L., 2010. Effect of cabin ventilation rate on ultrafine particle exposure inside automobiles. Environmental Science & Technology 44, 3546–3551.
Knibbs, L.D., de Dear, R.J., 2010. Exposure to ultrafine particles and $PM_{2.5}$ in four Sydney transport modes. Atmospheric Environment 44, 3224–3227.
Knol, A., de Hartog, J., Boogaard, H., Slottje, P., van der Sluijs, J., Lebret, E., Cassee, F., Wardekker, J.A., Ayres, J., Borm, P., Brunekreef, B., Donaldson, K., Forastiere, F., Holgate, S., Kreyling, W., Nemery, B., Pekkanen, J., Stone, V., Wichmann, H.E., Hoek, G., 2009. Expert elicitation on ultrafine particles: likelihood of health effects and causal pathways. Particle and Fibre Toxicology 6, 19.
Koutrakis, P., Sioutas, C., 1996. Physico-chemical properties and measurement of ambient particles. In: Wilson, Spengler (Eds.), Particles in Our Air: Concentrations and Health Effects. Harvard University Press, Boston, pp. 15–40.
Krausse, B., Mardaljevic, J., 2005. Patterns of drivers' exposure to particulate matter. In: Williams (Ed.), Spatial Planning, Urban Form and Sustainable Transport. Ashgate Publishing, Aldershot, pp. 151–167.
Larsson, B.M., Sehlstedt, M., Grunewald, J., Skold, C.M., Lundin, A., Blomberg, A., Sandstrom, T., Eklund, A., Svartengren, M., 2007. Road tunnel air pollution induces bronchoalveolar inflammation in healthy subjects. European Respiratory Journal 29, 699–705.
Larsson, B.M., Grunewald, J., Skold, C.M., Lundin, A., Sandstrom, T., Eklund, A., Svartengren, M., 2010. Limited airway effects in mild asthmatics after exposure to air pollution in a road tunnel. Respiratory Medicine 104, 1912–1918.

GL14 Continued

Baumbach, B.J., Rich, D.Q., Gandhi, S., Amorosa, L., Schneider, S., Zhang, J., Ohman-Strickland, P., Gong, J., Lelyanov, O., Kipen, H.M., 2010. Acute changes in heart rate variability in subjects with diabetes following a highway traffic exposure. Journal of Occupational and Environmental Medicine 52, 324–331.
Levy, J.I., Dumyahn, T., Spengler, J.D., 2002. Particulate matter and polycyclic aromatic hydrocarbon concentrations in indoor and outdoor microenvironments in Boston, Massachusetts. Journal of Exposure Analysis and Environmental Epidemiology 12, 104–114.
Li, N., Sioutas, C., Cho, A., Schmitz, D., Misra, C., Sempf, J., Wang, M., Oberley, T., Froines, J., Nel, A., 2003. Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage. Environmental Health Perspectives 111, 455–460.
Lin, E.J.S., Phuleria, H.C., Webber, W., Davey, M., Lawson, D.R., Ireson, R.G., Zielinska, B., Ondov, J.M., Weaver, C.S., Lapin, C.A., Easter, M., Hesterberg, T.W., Larson, T., 2010. Quantification of self pollution from two diesel school buses using three independent methods. Atmospheric Environment 44, 3422–3431.
Lorenz, T., Brunton, G., Oliver, S., Oliver, K., Oakley, A., 2008. Attitudes to walking and cycling among children, young people and parents: a systematic review. Journal of Epidemiology and Community Health 62, 852–857.
Marshall, J.D., Brauer, M., Frank, L.D., 2009. Healthy neighborhoods: walkability and air pollution. Environmental Health Perspectives 117, 1752–1759.
Marshall, J.D., 2008. Environmental inequality: air pollution exposures in California's South Coast Air Basin. Atmospheric Environment 42, 5499–5503.
McCreanor, J., Cullinan, P., Nieuwenhuijsen, M.J., Stewart-Evans, J., Malliarou, E., Jarup, L., Harrington, R., Svartengren, M., Han, I.K., Ohman-Strickland, P., Chung, K.F., Zhang, J., 2007. Respiratory effects of exposure to diesel traffic in persons with asthma. The New England Journal of Medicine 357, 2348–2358.
Moravska, L., Ristovski, Z., Jayaratne, E.R., Keogh, D.U., Ling, X., 2008. Ambient nano and ultrafine particles from motor vehicle emissions: characteristics, ambient processing and implications on human exposure. Atmospheric Environment 42, 5113–5128.
Nel, A., 2005. Air pollution-related illness: effects of particles. Science 308, 804–806.
Nieuwenhuijsen, M.J., Gómez-Perales, J.E., Colvile, R.N., 2007. Levels of particulate air pollution, its elemental composition, determinants and health effects in metro systems. Atmospheric Environment 41, 7995–8006.
Nystrom, A.K., Svartengren, M., Grunewald, J., Pousette, C., Rolin, L., Lundin, A., Skold, C.M., Eklund, A., Larsson, B.M., 2010. Health effects of a subway environment in healthy volunteers. European Respiratory Journal 36, 240–248.
Ott, W., Eliassen, R., 1973. A survey technique for determining the representativeness of urban air monitoring stations with respect to carbon monoxide. Journal of the Air Pollution Control Association 23, 685–690.
Ott, W., Klepeis, N., Switzer, P., 2008. Air change rates of motor vehicles and in-vehicle pollutant concentrations from secondhand smoke. Journal of Exposure Science and Environmental Epidemiology 18, 312–325.
Ott, W.R., 1985. Total human exposure. Environmental Science & Technology 19, 880–886.
Pattinson, W.J., 2009. Cyclist exposure to traffic pollution: microscale variance, the impact of route choice and comparisons to other modal choices in two New Zealand cities. MSc Thesis, University of Canterbury. Available online: http://ir.canterbury.ac.nz/bitstream/10092/3687/1/thesis_fulltext.pdf (accessed 13.12.10).
Peters, A., von Klot, S., Heier, M., Trentinaglia, I., Hormann, A., Wichmann, H.E., Lowel, H., 2004. Exposure to traffic and the onset of myocardial infarction. The New England Journal of Medicine 351, 1721–1730.
Phalen, R.F., Oldham, M.J., Nel, A.E., 2008. Tracheobronchial particle dose considerations for in vitro toxicology studies. Toxicological Sciences 92, 126–132.
Pooley, C., Whyatt, D., Walker, M., Davies, G., Coulton, P., Bamford, W., 2010. Understanding the school journey: integrating data on travel and environment. Environment and Planning A 42, 948–965.
Pui, D.Y.H., Qi, C., Stanley, N., Oberdorster, G., 2008. Recirculating air filtration significantly reduces exposure to airborne nanoparticles. Environmental Health Perspectives 116, 863–866.
Qi, C., Stanley, N., Pui, D.Y.H., Kuehn, T.H., 2008. Laboratory and on-road evaluations of cabin air filters using number and surface area concentration monitors. Environmental Science & Technology 42, 4128–4132.
Raut, J.C., Chazette, P., Fortain, A., 2009. Link between aerosol optical, microphysical and chemical measurements in an underground railway station in Paris. Atmospheric Environment 43, 860–868.
Riediker, M., Cascio, W.E., Griggs, T.R., Herbst, M.C., Bromberg, P.A., Neas, L., Williams, R.W., Devlin, R.B., 2004. Particulate matter exposure in cars is associated with cardiovascular effects in healthy young men. American Journal of Respiratory and Critical Care Medicine 169, 934–940.
Rim, D., Siegel, J., Spilchena, J., Webb, A., McDonald-Buller, E., 2009. Characteristics of cabin air quality in school buses in Central Texas. Atmospheric Environment 43, 6452–6464.
Ristovski, Z.D., Jayaratne, E.R., Lim, M., Ayoko, G.A., Morawska, L., 2006. Influence of diesel fuel sulfur on nanoparticle emissions from city buses. Environmental Science & Technology 40, 1314–1320.
Saksena, S., Prasad, R.K., Shankar, V.K., 2007. Daily exposure to air pollutants in indoor, outdoor and in-vehicle microenvironments: a pilot study in Delhi. Indoor and Built Environment 16, 39–46.
Saksena, S., Quang, T.N., Nguyen, T., Dang, P.N., Fischbein, P., 2008. Commuters' exposure to particulate matter and carbon monoxide in Hanoi, Vietnam. Transportation Research Part D: Transport and Environment 13, 209–215.
Samet, J.M., Rappold, A., Graff, D., Cascio, W.E., Bernstein, J.H., Huang, Y.C.T., Herbst, M., Bassett, M., Morelli, T., Hazucha, M.J., Bromberg, P.A., Devlin, R.B., 2009. Concentrated ambient ultrafine particle exposure induces cardiac changes in young healthy volunteers. American Journal of Respiratory and Critical Care Medicine 179, 1034–1042.
Seaton, A., Cherrie, J., Dennekamp, M., Donaldson, K., Hurley, J.F., Tran, C.L., 2005. The London underground: dust and hazards to health. Occupational and Environmental Medicine 62, 355–362.
Shrestha, K., 2009. An assessment of the contribution of micro-scale activities to personal pollution exposure in commuting microenvironments. MSc Thesis, University of Canterbury. Available online: http://ir.canterbury.ac.nz/bitstream/10092/3686/1/thesis_fulltext.pdf (accessed 13.12.10).
Strak, M., Boogaard, H., Meliefste, K., Oldenwening, M., Zuurbier, M., Brunekreef, B., Hoek, G., 2010. Respiratory health effects of ultrafine and fine particle exposure in cyclists. Occupational and Environmental Medicine 67, 118–124.
Stölzel, M., Breitner, S., Cyrys, J., Pitz, M., Wölke, G., Kreyling, W., Heinrich, J., Wichmann, H.E., Peters, A., 2007. Daily mortality and particulate matter in different size classes in Erfurt, Germany. Journal of Exposure Science and Environmental Epidemiology 17, 458–467.
Su, J.G., Morello-Frosch, R., Jesdale, B.M., Kyle, A.D., Shamasunder, B., Jerrett, M., 2009. An index for assessing demographic inequalities in cumulative environmental hazards with application to Los Angeles, California. Environmental Science & Technology 43, 7626–7634.
Thai, A., McKendry, I., Brauer, M., 2008. Particulate matter exposure along designated bicycle routes in Vancouver, British Columbia. Science of the Total Environment 405, 26–35.
Toone, C., Rowcrs, S., Armstrong, B.G., Kelly, F., Wilkinson, P., 2008. Air pollution and mortality benefits of the London Congestion Charge: spatial and socioeconomic inequalities. Occupational and Environmental Medicine 65, 620–627.
Vinzents, P.S., Moller, P., Sorensen, M., Knudsen, L.E., Hertel, O., Jensen, F.P., Schibye, B., Loft, S., 2005. Personal exposure to ultrafine particles and oxidative DNA damage. Environmental Health Perspectives 113, 1485–1490.
Wallace, L., Ott, W., 2011. Personal exposure to ultrafine particles. Journal of Exposure Science and Environmental Epidemiology 21, 20–30.
Weichenthal, S., Dufresne, A., Infante-Rivard, C., 2007. Indoor ultrafine particles and childhood asthma: exploring a potential public health concern. Indoor Air 17, 81–91.
Weichenthal, S., Dufresne, A., Infante-Rivard, C., Joseph, L., 2008. Determinants of ultrafine particle exposures in transportation environments: findings of an 8-month survey conducted in Montreal, Canada. Journal of Exposure Science and Environmental Epidemiology 18, 551–563.
Weisel, C.P., 2004. Transportation. In: Spengler, Samet, McCarthy (Eds.), Indoor Air Quality Handbook. McGraw-Hill, New York, pp. 68.1–68.20.
Westerdahl, D., Fruin, S., Sax, T., Fine, P.M., Sioutas, C., 2005. Mobile platform measurements of ultrafine particles and associated pollutant concentrations on freeways and residential streets in Los Angeles. Atmospheric Environment 39, 3597–3610.
Wichmann, H.E., Peters, A., 2009. Epidemiological evidence of the effects of ultrafine particle exposure. Philosophical Transactions of the Royal Society of London. Series A: Mathematical, Physical and Engineering Sciences 358, 2751–2769.
Xu, B., Zhu, Y., 2009. Quantitative analysis of the parameters affecting in-cabin to on-roadway (I/O) ultrafine particle concentration ratios. Aerosol Science and Technology 43, 400–410.
Xu, B., Lin, S., Zhu, Y., 2010. Ultrafine particle penetration through idealized vehicle cracks. Journal of Aerosol Science 41, 859–868.
Zhang, Q., Zhu, Y., 2010. Measurements of ultrafine particles and other vehicular pollutants inside school buses in South Texas. Atmospheric Environment 44, 255–261.
Zhu, Y., Figuero-Fernandez, A., Hinds, W.C., Miguel, A.H., 2007. In-cabin commuter exposure to ultrafine particles on Los Angeles freeways. Environmental Science & Technology 41, 2138–2145.
Zhu, Y., Fung, D., Kennedy, N., Hinds, W.C., Figuren-Fernandez, A., 2008. Measurements of ultrafine particles and other vehicular pollutants inside a mobile exposure system on Los Angeles freeways. Journal of the Air & Waste Management Association 58, 424–434.
Zuurbier, M., Hoek, G., Van den Hazel, P., Brunekreef, B., 2009. Minute ventilation of cyclists, car and bus passengers: an experimental study. Environmental Health 8, 48.
Zuurbier, M., Hoek, G., Oldenwening, M., Lenters, V., Meliefste, K., van den Hazel, P., Brunekreef, B., 2010. Commuters' exposure to particulate matter air pollution is affected by mode of transport, fuel type, and route. Environmental Health Perspectives 118, 783–789.
Zuurbier, M., Hoek, G., Oldenwening, M., Meliefste, K., van den Hazel, P., Brunekreef, B., 2011. Respiratory effects of commuters' exposure to air pollution in traffic. Epidemiology 22, 219–227.

GL14 Continued

PERGAMON

Atmospheric Environment 36 (2002) 4323–4335

ATMOSPHERIC ENVIRONMENT

www.elsevier.com/locate/atmosenv

Study of ultrafine particles near a major highway with heavy-duty diesel traffic

Yifang Zhu[a], William C. Hinds[a,*], Seongheon Kim[b], Si Shen[c], Constantinos Sioutas[c]

[a] Department of Environmental Health Sciences, University of California Los Angeles, 650 Charles E. Young Drive South, Los Angeles, CA 90095, USA

[b] School of Earth and Environmental Sciences (BK21), Seoul National University, Seoul, South Korea

[c] Department of Civil and Environmental Engineering, University of Southern California, 3620 South Vermont Avenue, Los Angeles, CA 90089, USA

Received 6 March 2002; accepted 29 May 2002

Abstract

Motor vehicle emissions usually constitute the most significant source of ultrafine particles (diameter <0.1 μm) in an urban environment. Zhu et al. (J. Air Waste Manage. Assoc., 2002, accepted for publication) conducted systematic measurements of the concentration and size distribution of ultrafine particles in the vicinity of a highway dominated by gasoline vehicle. The present study compares these previous measurements with those made on Interstate 710 freeway in Los Angeles. The 710 freeway was selected because more than 25% of the vehicles are heavy-duty diesel trucks. Particle number concentration and size distribution in the size range from 6 to 220 nm were measured by a condensation particle counter and a scanning mobility particle sizer, respectively. Measurements were taken at 17, 20, 30, 90, 150, and 300 m downwind and 200 m upwind from the center of the freeway. At each sampling location, concentrations of carbon monoxide (CO) and black carbon (BC) were also measured by a Dasibi CO monitor and an Aethalometer, respectively. The range of average concentration of CO, BC and total particle number concentration at 17 m was 1.9–2.6 ppm, 20.3–24.8 μg/m^3, 1.8×10^5–3.5×10^5/cm^3, respectively. Relative concentration of CO, BC and particle number decreased exponentially and tracked each other well as one moves away from the freeway. Both atmospheric dispersion and coagulation appears to contribute to the rapid decrease in particle number concentration and change in particle size distribution with increasing distance from the freeway. Average traffic flow during the sampling periods was 12,180 vehicles/h with more than 25% of vehicles being heavy-duty diesel trucks. Ultrafine particle number concentration measured at 300 m downwind from the freeway was indistinguishable from upwind background concentration. These data may be used to estimate exposure to ultrafine particles in the vicinity of major highways.

Keywords: Ultrafine particles; Freeways; Diesel; Carbon monoxide; Black carbon

1. Introduction

Epidemiological data from air pollution studies have shown a consistent relationship between increases in particulate matter (PM) exposure and contemporary increases in mortality and morbidity (Schwartz, 1991; Dockery et al., 1993; Pope et al., 1995; Vedal, 1997). However, the underlying biological causes of the health effects of PM exposure and the correct measurement metric are unclear. For example, it is not clear whether the mass concentration (Osunsanya et al., 2001) or the number concentration (Peters et al., 1997; Penttinen et al., 2001) is most important in causing these adverse

*Corresponding author.
E-mail address: whinds@ucla.edu (W.C. Hinds).

PII: S1352-2310(02)00354-0

GL14 Continued

PM health effects. Currently, there are several hypotheses used to explain the association of PM and observed adverse health effect. One argues that particle surface contaminants, such as transition metals, contribute towards ill health (Fubini et al., 1995; Gilmour et al., 1996), wherein the ultrafine particles are thought to act as vehicles for those contaminants, initiating local lung damage when the particles deposit on the epithelial surfaces. Another hypothesis is that the physical characteristics (e.g. number, size, shape, aggregation properties) are important in producing health effects (Bérubé et al., 1999). Particle shape and size are critical factor controlling where the inhaled particles deposit in the various regions of human respiratory system by the complex action of aerosol deposition mechanisms (Hinds, 1999).

Recent toxicological studies have concluded that ultrafine particles (diameter <100 nm) are more toxic than larger particles with the same chemical composition and at the same mass concentration (Ferin et al., 1990; Oberdörster, 1996, 2001; Donaldson et al., 1998, 2001; Churg et al., 1999; Brown et al., 2000). Currently, however, only the mass concentration of PM $<10\,\mu$m in aerodynamic diameter (PM_{10}) and $<2.5\,\mu$m ($PM_{2.5}$) are regulated. Information about ultrafine particles is usually not available. In fact, even though ultrafine particles represent over 80% of particles in terms of number concentration in an urban environment (Morawska et al., 1998a, b), the less numerous but much heavier particles of the accumulation (0.1–2 μm) and coarse (2.5–10 μm) modes dominate mass concentration measurements. Thus, number concentration, together with the size distribution of ultrafine particles, is needed to better assess ambient air quality and its potential health effects.

Emission inventories suggest that motor vehicles are the primary direct emission sources of fine and ultrafine particles to the atmosphere in urban areas (Schauer et al., 1996; Shi et al., 1999; Hitchins et al., 2000). Although traffic-related air pollution in urban environments has been of increasing concern, most studies have focused on gaseous pollutants, total mass concentration, or chemical composition of particulate pollutants (Kuhler et al., 1994; Clairborn et al., 1995; Williams and McCrae, 1995; Janssen et al., 1997; Roorda-Knape et al., 1998a, b; Wrobel et al., 2000). Booker (1997) found that particle number concentration was strongly correlated with vehicle traffic while PM_{10} was essentially uncorrelated with traffic. Since the majority of particle number from vehicle exhaust are in the size range 20–130 nm for diesel engines (Morawska et al., 1998a, b) and 20–60 nm for gasoline engines (Ristovski et al., 1998), it is important and necessary to quantify ultrafine particle emission levels, and to determine ultrafine particle behavior after emission as they are transported away from the emission source—busy roads and freeways.

Morawska et al. (1999) measured the horizontal and vertical profiles of submicrometer particulates (16–626 nm) near a major arterial route in the urban area of Brisbane, Australia. They found, with the exception of measurements in close proximity to the road (about 15 m), that the horizontal ground-level profile measurements did not show statistically significant differences in fine particle number concentration for up to 200 m distances away from the road. Hitchins et al. (2000) examined the particle size distribution and concentration in the size range from 15 nm to 20 μm at distances from a road ranging from 15 to 375 m at two sites in Australia. They conducted measurements under different wind conditions and found that when the wind is blowing directly from the road, the concentration of the fine and ultrafine particles decayed to about half of their maximum at a distance of 100–150 m from the road. Shi et al. (1999) measured ultrafine particle number concentrations and size distributions at a busy roadside and at nearby urban background sites in Birmingham, United Kingdom. They observed a faster decline of particle number concentration than mass concentration. In a recent study, Shi et al. (2001) reported that the fraction of particles <10 nm represents more than about 40% of the total particle number concentrations at 4 and 25 m from the roadside curb.

While there have been recent studies of ultrafine particles from traffic in other countries, except for Zhu et al. (2002), no comparable work has been done in the Los Angeles basin, a home to more than 15 million individuals and 10 million vehicles contributing to daily traffic. Previous studies have shown that meteorological conditions may affect substantially the characteristics of PM emitted from vehicles. Kittelson et al. (2001) found in their on-road PM measurements that the concentration of particles in the nuclei mode increases by nearly a factor of 10 as the (air) temperature is reduced from 25°C to 15°C. This observation suggests that there could be significant differences in the tendency to form semi-volatile nanoparticles between, for example, northern Europe and Southern California.

Zhu et al. (2002) conducted a systematic ultrafine particle study near one of the busiest freeways in the Los Angeles basin, Interstate 405. Traffic on that freeway was dominated by gasoline-powered cars and light trucks, with <5% of vehicles being heavy-duty diesel trucks. In the US, spark ignition vehicles usually account for most of the vehicles operating on highways. However, since diesel vehicles emit more PM on a fleet averaged, gram-per-vehicle mile mass basis (Kittelson et al., 2001), and that diesel engine exhaust has been proposed as carcinogen in animals and probably carcinogenic for humans (IARC, 1989), it is necessary and timely to conduct a comprehensive study of ultrafine particles in the vicinity of a diesel vehicle dominated freeway. Thus, the aim of the present paper is

GL14 Continued

to systematically evaluate ultrafine particles in the vicinity of the 710 freeway in the Los Angeles basin, a freeway where more than 25% of vehicles are heavy-duty diesel trucks. Particle number concentration and size distribution in the size range from 6 to 220 nm are measured along with CO and black carbon (BC) as a function of distances upwind and downwind the 710 freeway. The results from the current study are compared to those by Zhu et al. (2002) which were obtained near the 405 freeway.

2. Experimental

2.1. Description of sampling site

This study was conducted in the City of Downey along Southern Avenue between 30 August and 27 October 2001. The location was chosen for its proximity to the freeway and the lack of other nearby ultrafine particle emission sources. Southern Avenue is located perpendicular to Interstate 710 Freeway and Garfield Avenue near the Los Amigos Country Club. Freeway 710 runs generally north and south near the sampling site and parallels the Los Angeles River.

This location is ideal for this study for several reasons. First, there are no other major roadways near the sampling sites along Southern Avenue. Second, businesses along Southern Avenue generally have large open land areas with little activities during the day. Thus, there is minimal local traffic influence at the sampling locations. Third, the freeway is at the same elevation as Southern Avenue. The only separation between the freeway and Southern Avenue is a metal chain link fence along the freeway. This allowed measurements as close as 3 m from the edge of the freeway. Fourth, a nearby residential area approximately 200 m upwind from the freeway was easily accessible for sampling.

During the sampling period, a fairly consistent eastward wind developed each day starting at approximately 11:00 AM. This wind carried the freeway vehicular emissions directly to the sampling location. The 710 freeway has eight lanes, four north bound and four south bound. It is approximately 26 m wide including a 1-m-wide median strip. Measurement site locations for this study were designated by their distance from the center of the median strip. Thus, the distance from each sampling location to the nearest traffic lane is 13 m less than the indicated distance.

Freeway 710 is a major truck route in Southern California with a large percent of the traffic consisting of heavy-duty diesel trucks. During the sampling period, traffic density ranged from 180 to 230 vehicles/min passing the sampling site, total for both directions, with approximately 25% of the vehicles being heavy diesel trucks.

2.2. Sampling and instrumentation

Wind speed and direction were measured at a fixed site 6 m above the ground level 20 m downwind of 710 freeway, which also served as a particle number concentration control site. Wind data were averaged over 1 min intervals and logged into a computerized weather station (Wizard III, Weather Systems Company, San Jose, CA). Throughout each measurement period, the traffic strength on the freeway, defined as number of vehicles passing per minute, was continuously monitored by a video recorder (camcorder), which captures all eight lanes of the freeway. After each sampling session, the videotapes were replayed and traffic density counted manually. Three 1-min samples were randomly selected from each 10-min interval. Cars, light trucks, and heavy-duty trucks were counted separately to estimate the traffic density by type of vehicle.

Particle number concentration and size distribution in the size range from 6 to 220 nm were measured by a condensation particle counter (CPC 3022A; TSI Inc., St. Paul, MN) and a scanning mobility particle sizer (SMPS 3936, TSI Inc., St. Paul, MN). The sampling flow rate of the SMPS was adjusted to 1.5 lpm in order to measure particles as low as 6 nm as well as to minimize the diffusion losses of ultrafine particles during sampling. Flexible, conductive tubing (Part 3001940, TSI Inc., St. Paul, MN) was used for sampling to avoid particle losses due to electrostatic forces. The sizing accuracy of the SMPS was verified in the laboratory by means of monodisperse polystyrene latex spheres (PSL, Polysciences Inc., Warrington, PA). Data reduction and analysis of the SMPS output was done by the Aerosol Instrument Manager software (version 4.0, TSI Inc., St. Paul, MN). Measurements were taken at 17, 20, 30, 90, 150, and 300 m downwind and 200 m upwind from the center of the freeway 710. At each location, three size distribution samples were taken in sequence with the SMPS. Scanning time for each was 180 s.

In addition to size distribution and the total number concentration, the concentrations of BC and carbon monoxide (CO), were monitored simultaneously at each sampling location. Before each measurement session, all instruments were time synchronized. Data were averaged after collection over the time periods corresponding to the scanning intervals of the SMPS. A Dual Beam Aethalometer (Model AE-20, Andersen Model RTAA-900, Andersen Instruments Inc., Smyrna, GA) was used to measure the BC concentrations every 5 min. Concentrations of CO were measured by a near-continuous CO monitor (Dasibi Model 3008, Environmental Corp., Glendale, CA) every minute. The CO monitor was calibrated by means of standard CO gas (RAE systems Inc., Sunnyvale, CA) in the laboratory and automatically zeroed each time the power was turned on.

GL14 Continued

Electric power for the control site CPC and Weather Station was obtained by an extension cord to a nearby office. Electric power for other sampling instruments at the sampling locations was supplied by a 1.2 kW gasoline-powered portable power generator (Model EU 1000i, Honda Motor Co., LTD., Tokyo, Japan). The generator was placed approximately 50 m downwind of each sampling location. Both total particle number and CO concentrations were measured at the control site with the generator turned on and with it turned off. No detectable difference was observed.

Table 1 gives the sampling dates and times and summarizes the instruments that were used on each date. The weather station and control CPC were placed at the 20 m downwind control site and sampled throughout the sampling period each day. All other applicable instruments were moved together and sampled simultaneously at each sampling location. It takes about 10 min to complete sampling at each location and 120 min to complete a set, all six locations. Three to four sets were performed on each sampling date.

3. Results and discussion

The results presented below include measurements of total particle number concentrations by a control CPC, wind velocity by a Weather Wizard III, both positioned at a fixed location 20 m downwind of the freeway; and CO, BC concentration, and ultrafine particles size distributions upwind and at six downwind distances from freeway 710.

3.1. Wind effects

Changes in wind conditions have been reported to modify dramatically the pattern of total particle number concentration versus distances from a major road (Hitchins et al., 2000). Consistency in wind speed and direction allows data from different days to be averaged together (Zhu et al., 2002). Wind speed and direction were measured, averaged and logged over every 1-min interval throughout each sampling period. One hundred wind data points were randomly selected out of more than 5000 observations from all the sampling dates and plotted in Fig. 1. The orientation of freeway 710 and the sampling road, Southern Avenue, are also shown in the Fig. 1. The Weather Wizard III instrument recorded wind direction at a 22.5° interval (e.g. 11.25° on either side of N, NNE, etc.) and wind speed at 0.4 or 0.5 m/s intervals. In the figure, duplicate observations were spread out slightly in both directions to better illustrate how strong the wind was and how often the wind came from certain directions. Based on all 5000 observations, the percent of sampling time that the wind came from each 22.5° segment is also shown in Fig. 1. As shown in Fig. 1, about 80% of the time, the wind was coming directly from the freeway towards the sampling road with a speed <3 m/s. The consistency of observed wind direction and speed is a result of a generally low synoptic wind velocities and a consistent sea breeze in the sampling area.

In this study, we found that not only wind direction, but also wind speed, played an important role in determining the characteristics of ultrafine particles near the 710 freeway, similar to the observations made by Zhu et al. (2002) near the 405 freeway. However the pattern of total particle number concentrations as a function of wind speed is somewhat different for the two studies. Fig. 2 shows total particle number concentrations measured by the control CPC, located 20 m downwind of the 710 freeway versus wind speed. Averaged data for the 405 freeway from Zhu et al. (2002) are also plotted for comparison. The CPC was programmed to archive averaged total particle number concentrations at 1-min interval in synchronization with the averaging time of the meteorological data. Only wind data within ±22.5° of normal to the freeway was used in this figure which accounts for more than 60% of the total observations. The difference between the absolute value of total particle number concentration is due in part to the difference in the sampling distance. The control CPC was located 20 m downwind from the 710 freeway but 30 m from the 405 freeway. Assuming the fitted exponential decay characteristics of ultrafine particles holds right to the edge of the freeway, it is thus not surprising, as discussed below, that the CPC will read a greater total particle number concentration at 20 m in the present study than at 30 m in that by Zhu et al. (2002), given similar traffic load on both freeways. However, the relative particle number concentration as function of wind speed are somewhat different in these two studies. The relative particle number concentration decreased as the wind speed increased near the 405 freeway. In contrast, particle number concentration in the 710 freeway first increases, reaches a maximum around 1.5 m/s, and then decreases. There is no obvious explanation for the observed difference. In both studies, data showed large error bars, and the data of low wind speed (<1 m/s) were very limited. In addition, the 405

Table 1
Sampling dates, time and instruments used

Date	Time	Weather Wizard III	Control CPC	SMPS	CO monitor	Aethalometer
08/30/01	10:00–15:30	×	×	×	×	×
09/05/01	10:30–16:00	×	×	×		
09/21/01	10:00–15:00	×	×	×	×	×
09/25/01	10:30–16:00	×	×	×	×	×
10/05/01	10:30–16:00	×	×	×	×	×
10/24/01	10:00–15:30	×	×		×	×
10/30/01	10:00–15:30	×	×	×		

GL14 Continued

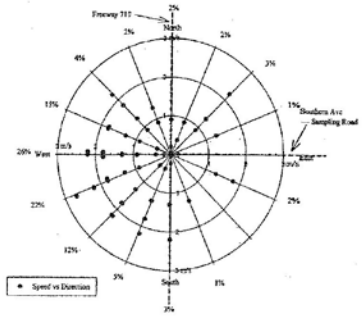


Fig. 1. Wind direction and speed at sampling site.

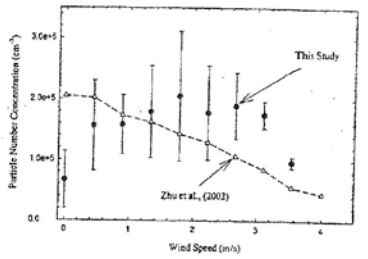


Fig. 2. Total particle number concentration measured by CPC located at 20 m downwind from freeway 710 versus wind speed. Bars indicate one standard deviation.

GL14 Continued

freeway is elevated approximately 4.5 m above the surrounding terrain, while, the 710 freeway is at ground level, the same as the sampling location. Lower speed wind would be expected to cause less atmospheric dilution, and thus lead to greater particle number concentrations, as Zhu et al. (2002) reported. However, at extremely low wind speeds, it would take a considerably longer time for the wind to carry particles to the sampling port of the CPC, which gives ultrafine particles more time to coagulate with either themselves or with larger particles, a phenomenon that would decrease the total particle number concentration. This may partially explain the observed "n" shape curve in the current study.

3.2. Traffic effects

The portion of freeway 710 passing through the City of Downey is a major truck shipping route. The average traffic volume per hour during the measurement period was: 8730 cars, 870 light trucks, 2580 heavy trucks, and 12180 total vehicles. It is apparent from these numbers that diesel emission vehicles on the 710 freeway represent about 30% of vehicles while on the 405 freeway they represent <5% (Zhu et al., 2002). Fig. 3 compares the traffic volume on both the 405 and the 710 freeways. Error bars represent one standard deviation. It is seen that the 710 freeway has about 7 times as many diesel vehicles and 70% of gasoline vehicles as the 405 freeway. The total vehicle numbers on both freeways are quite similar 12,180 versus 13,900/h for the 405 freeway.

Zhu et al. (2002) reported that a traffic slowdown on freeway 405 was associated with a drop in total particle number concentration indicating that fewer ultrafine particles are emitted during such events. In this study, the traffic speed on the 710 freeway stayed constant through out the sampling period. No traffic slow down was observed. The difference in the variability of traffic volume on both freeways is indicated by the error bars in Fig. 3.

Zhu et al. (2002) reported that both wind speed and traffic density affected the characteristics of ultrafine particles near the 405 freeway, and the control CPC responded to these effects reasonably well. Thus, subsequent data for ultrafine particle analysis at increasing distances from the freeway were all normalized to the control CPC's reading. An average CPC reading, $\overline{C_N}$, was obtained based on all the measurements. In Figs. 4–6, number concentration and size distribution data were scaled to $\overline{C_N}$ by dividing each measurement by the ratio of CPC reading for the period of measurement to $\overline{C_N}$.

3.3. Change in ultrafine particle size distribution with increasing distance

Fig. 4 depicts ultrafine particle size distributions at 17, 20, 30, 90, 150 and 300 m downwind and 300 m upwind of freeway 710. The size distributions are smoothed and shown together with common scales for both axes. The horizontal axis represents particle size on a logarithmic scale, while the vertical axis represents normalized particle number concentration in the size range of 6–220 nm as measured by the SMPS. Data were averaged for all applicable sampling dates for each distance from the freeway. As shown in Fig. 4, ultrafine particle size

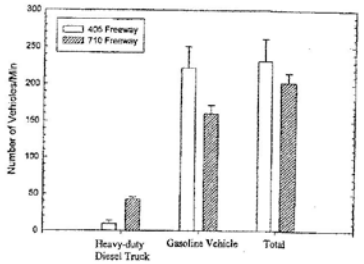


Fig. 3. Traffic volume compariton for the 405 and 710 freeway. Bars indicate one standard deviation.

GL14 Continued

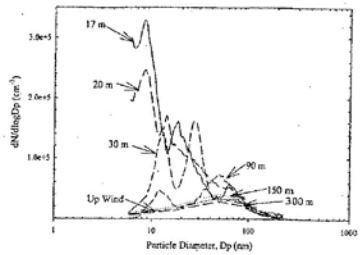


Fig. 4. Ultrafine particle size distribution at different sampling locations near the 710 freeway.

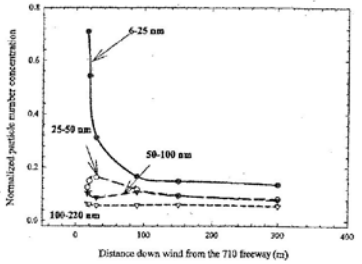


Fig. 5. Normalized particle number concentration for different size ranges as a function of distance from the 710 freeway.

distribution changed markedly and its number concentration dropped dramatically with increasing distance. At the nearest sampling location, 17 m downwind from the center of the freeway, the dominant mode was around 10 nm with a modal concentration of more than 3.2×10^5/cm^3. This mode remained at 10 nm for the second sampling location, 20 m downwind from the freeway, but its concentration dropped to 2.4×10^5/cm^3. It shifted to larger size range and its concentration kept decreasing for farther sampling locations. This mode was not observed at distance >150 m downwind from the freeway. The dramatic decrease of particle number concentration in the size range around 10 nm was likely due to atmospheric dilution and several atmospheric aerosol particle loss mechanisms that favor small particles, diffusion to surfaces, evaporation, and coagulation. The smaller the particle, the greater its diffusion coefficient and its Brownian motion. Particles of 10 nm diffuse about 80 times faster than particles of 100 nm (Hinds, 1999). As particle size gets smaller, the Kelvin effect becomes more important, making it easier for molecules to leave the particle's surface by evaporation. In addition, when two small particles collide due to their Brownian motion (coagulate), they form a bigger particle. Thus, coagulation reduces number concentrations and shifts the size distribution to larger sizes.

GL14 Continued

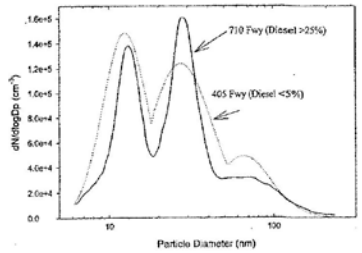


Fig. 6. Comparison of ultrafine particle number concentration at 30 m downwind from 405 and 710 freeway.

In Fig. 4, the second mode at 17 m downwind from the freeway was around 20 nm with a concentration of 1.5×10^5/cm^3. This mode remained at similar size range and concentration for the next sampling location, 20 m, but shifted to 30 nm at 30 m downwind from the freeway. It is of particular note that, while the concentration for the primary mode, 10 nm mode, decreased about 60% of its maximum value from 17 to 30 m with a slight shift in its mode, the 20 nm mode concentration did not change significantly but the modal size shifted noticeably. This second mode continued to shift to larger sizes with increasing distance from the freeway. In general number concentrations for smaller particles, $d_p < 50$ nm, dropped significantly with increasing distances from the freeway, but for larger ones, $d_p > 100$ nm, number concentrations decreased only slightly. These results are in excellent agreement with what Zhu et al. (2002) reported for freeways impacted mostly by gasoline vehicles, which suggests that coagulation is more important than atmospheric dilution for the smallest ultrafine particles and vice versa for large particles. Ultrafine particle concentrations measured at 150 and 300 m downwind of the 710 freeway were statistically within the variation of the 300 m upwind background concentration. The maximum number concentration that was observed next to the freeway was about 30 times greater than that for the background location. This suggests that people who live or work within 100 m downwind of major traffic sources, or spend a substantial amount of time commuting on such highways, will have a much higher ultrafine particle exposure than those who do not. This result can be used in epidemiological studies to estimate exposure to ultrafine particles.

Based on Fig. 4, it is clear that vehicle-emitted ultrafine particles of different size ranges behave quite differently in the atmosphere. Zhu et al. (2002) showed the decay of ultrafine particle number concentrations in four size ranges 6–25, 25–50, 50–100 and 100–220 nm. They found coagulation played a significant role in modifying the particle size distribution of vehicle-emitted ultrafine particle downwind of a freeway. Fig. 5 was prepared in the same ways as Zhu et al. (2002). The measured particle number concentrations in each SMPS size bin were combined in the corresponding size range, and the result was normalize to averaged wind speed. The general trends of sub-grouped ultrafine particle decay curves are quite comparable to those given by Zhu et al. (2002), Figs. 7a and b. Total particle number concentration in the size range of 6 to 25 nm accounted for about 70% of total ultrafine particle number concentration and dropped sharply, by about 80%, at 100 m, and leveled off after 150 m. Overall, it decayed exponentially through out the whole measured distance. Number concentrations in the next two size ranges 25–50 and 50–100 nm, all experienced a shoulder between 17 and 150 m. These results are in excellent agreement with what Zhu et al. (2002) observed and can be explained by particles, in smaller size ranges, coagulating with these particles to increase their size.

Fig. 5 compares the ultrafine particle size distributions at 30 m downwind from the 710 and the 405 freeways. Three-mode lognormal fitting was used for 405 freeway. Raw data were smoothed by averaging for 710 freeway. Heavy-duty diesel trucks on the 710 freeway represent more than 25% of traffic while on the 405 freeway they represent <5% (Zhu et al., 2002). Average PM emission rate for heavy-duty diesel trucks is about 0.4 g/mi (California ARB, 2000) while for passenger cars is

GL14 Continued

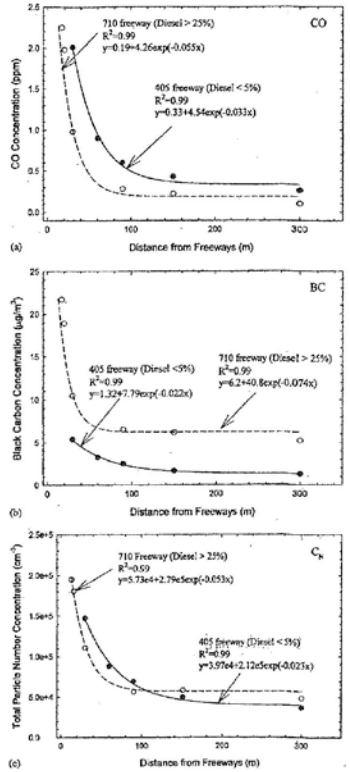


Fig. 7. Decay curves of: (a) CO, (b) BC and (c) particle number concentration near the 405 and 710 freeway.

GL14 Continued

about 0.08 g/mi (EPA, 2000). Thus, on the 710 freeway, about 60% of PM emission is due to heavy-duty diesel trucks ($(0.25 \times 0.4)/(0.25 \times 0.4 + 0.75 \times 0.08) = 62.5\%$). In Fig. 6, both size distributions have three distinct modes. The concentration for the first mode, between 10 to 20 nm, is slightly higher near the 405 freeway. This mode is likely to arise from homogeneous nucleation of semi-volatile materials and is similar to that previously reported for direct laboratory measurement of gasoline vehicle emissions (Ristovski et al., 1998). The concentration for the second mode, around 30 nm, is about 30% higher near the 710 freeway than that near the 405 freeway. This mode probably comprises mainly of BC and is likely due to the much higher diesel emissions on the 710 freeway. The last mode, around 70 nm, represents an insignificant contribution to number concentrations for these two freeways and in both cases are comparable to the background concentrations.

3.4. Decay of carbon monoxide, black carbon and particle number concentration

To make this freeway study more comprehensive, the concentrations of CO, BC, and particle number were also measured at increasing distance from the freeway on selected dates, as shown in Table 1. CO and BC were intentionally selected because their ambient concentrations are closely related to vehicular emissions. Averaged concentration and range of values at different distances from the freeway of each measured property are summarized in Table 2. CO and BC concentrations decreased noticeably when moving away from the traffic sources, similar to the findings of the study by Zhu et al. (2002).

Figs. 7a–c were prepared by comparing the decay characteristic of CO, BC and particle number concentrations near the 405, gasoline vehicle dominated, and the 710, diesel vehicle dominated, freeways. Exponential decay was found to be a good estimator for predicting total particle number concentrations at different locations (Zhu et al., 2002). Each data point in the figure represents an averaged value for all measurements with similar wind directions. The solid line was the best fitting exponential decay curve, determined using SigmaPlot 2000 nonlinear curve fitting procedure. The best fitting exponential decay equations and R^2 values are also given in the figure. It can be seen, in general, all three pollutants decay at a similar rate near both freeways. This implies that atmospheric dilution plays a comparable role in both studies. As discussed previously, the average wind speed for these two studies are all close to 1.5 m/s. The discrepancies of the curves were mainly due to the different traffic fleet compositions on these two freeways. The 710 freeway has more than 25% heavy diesel trucks while the 405 freeway has <5%. It is well known that diesel engines emit less CO and more BC comparing to spark ignition engines (Kittelson et al., 2001). Fig. 7a shows that the concentration of CO near the 710 freeway is generally half of that near the 405 freeway. By comparison, Fig. 7b shows the BC concentration near a diesel vehicle dominated freeway is more than three times greater than that near a gasoline vehicle dominated freeway. As shown in Fig. 7c, the total particle number concentration close to the 405 freeway is somewhat higher than that near the 710 freeway, but drops faster with downwind distance. Since the rate of coagulation increases with decreasing particle size down to 20 nm (Hinds, 1999), the observed result suggests more of the smallest ultrafine particles, mostly in nano-size range, were emitted from the 405 freeway. This may be explained by a total of 20% more vehicles on the 405 freeway. It was previously reported that number emission rates from the spark-ignition vehicles were much lower than from the diesel vehicles under most operating conditions, but were similar under high-speed highway cruise conditions (Rickeard et al., 1996; Kittelson, 1998). It should also be noted that the exponential decay characteristic appears to extend to about 3 m downwind from the edge of the freeway for all three pollutants. Based on our results we conclude that atmospheric dilution is so rapid that average concentration decays continuously after leaving the tailpipe.

Table 2
Measured averaged concentrations at increasing distances from the freeway[a]

Measurement	Upwind (m)	Downwind distance (m)					
	200	17	20	30	90	150	300
CO (ppm)	0.1 (0.0–0.2)	2.3 (1.9–2.6)	2.0 (1.5–2.4)	1.7 (1.1–1.9)	0.5 (0.2–0.7)	0.4 (0.1–0.5)	0.2 (0.1–0.3)
Black carbon ($\mu g/m^3$)	4.6 (3.1–5.9)	21.7 (20.3–24.8)	19.4 (16.5–21.5)	17.1 (12.6–19.3)	7.8 (4.5–9.3)	6.5 (2.9–9.2)	5.5 (3.5–7.7)
Number concentration ($\times 10^{-5}$/cm^3)	0.48 (0.36–0.57)	2.0 (1.8–2.5)	1.8 (1.5–2.5)	1.6 (1.2–1.9)	0.72 (0.42–1.1)	0.61 (0.35–0.98)	0.49 (0.30–0.59)

[a] Range given in parenthesis.

GL14 Continued

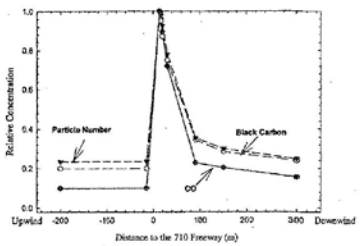


Fig. 8. Relative particle number, BC, CO concentrations versus distance from the 710 freeway.

Fig. 8 shows the decay curves for relative concentrations of CO, BC and total particle number. The curves are normalized and extended to reach 1.0 at the downwind edge of the 710 freeway. Background concentrations are also shown in the figure. It is seen that CO, BC and particle number concentration decreased about 60–80% in the first 100 m and then leveled off somewhat after 150 m, similar to what Zhu et al. (2002) reported. Background CO has a much lower relative concentration while background BC and particle number concentrations are comparable. Thus, CO was diluted more quickly and significantly than BC and particle number concentration. In general, CO, BC and particle number concentrations tracked each other very well. These results confirm the common assumption that vehicular exhaust is the major source for CO, BC and ultrafine particles near a busy freeway. They also support the conclusion made by Zhu et al. (2002) that for the conditions of these measurements the decreasing characteristics of any of these three pollutants could be used interchangeably to estimate the relative concentration of the other two pollutants near freeways.

4. Conclusions and summary

Wind speed and direction are important in determining the characteristic of ultrafine particles near freeways. The average concentrations of CO, BC and particle number concentration at 17 m was 1.9–2.6 ppm, 20.3–24.8 $\mu g/m^3$, 1.8×10^5–3.5×10^5/cm^3, respectively. Relative concentration of CO, BC and particle number tracked each other well as one moves away from the freeway. Exponential decay was found to be a good estimator for the decrease of these three pollutants' concentration with distance along the wind direction starting from the edge of the freeway. Measurements show that both atmospheric dilution and coagulation play important roles in the rapid decrease of particle number concentration and the change in particle size distribution with distance away from a freeway.

Acknowledgements

This work was supported by the Southern California Particulate Center and Supersite: US Environmental Protection Agency under grant number R82735201, and California Air Resources Board under contract number 98-316. The authors also would like to thank Mr. Yuqing Zhang, for his assistance with the field measurement.

References

Bérubé, K.A., Jones, T.P., Williamson, B.J., Winters, C., Morgan, A.J., Richards, R.J., 1999. Physicochemical characterization of diesel exhaust particles: factors for assessing biological activity. Atmospheric Environment 33, 1599–1614.

Boeker, D.R., 1997. Urban pollution monitoring. Oxford City Centre. Research Report, AEA Technology, Aerosol Science Centre, Oxfordshire, UK.

Brown, D.M., Stone, V., Findlay, P., Macnee, W., Donaldson, K., 2000. Increased inflammation and intracellular calcium caused by ultrafine carbon black is independent of transition metals or other soluble components. Occupational and Environmental Medicine 57 (10), 685–691.

California Environment Protection Agency, Air Resource Board, 2000. Public meeting to consider approval of revisions to the state's on-road motor vehicle emissions inventory. Technical Support Document.

GL14 Continued

Churg, A., Gilks, B., Dai, J., 1999. Induction of fibrogenic mediators by fine and ultrafine titanium dioxide in rat tracheal explants. American Journal of Physiology—Lung Cellular and Molecular Physiology 277(5), 21–5, L975–L982.

Claiborn, C., Mitra, A., Adams, G., Bamesberger, L., Allwine, G., Kantamaneni, R., Lamb, B., Westberg, H., 1995. Evaluation of PM_{10} emission rates from paved and unpaved roads using tracer technique. Atmospheric Environment 29, 1075–1089.

Dockery, D.W., Pope, A., Xu, X., Spengler, J.D., Ware, J.H., Fay, M.E., Ferris, B.G., Speizer, F.E., 1993. An association between air pollution and mortality in six us cities. New England Journal of Medicine 329, 1753–1759.

Donaldson, K., Li, X.Y., MacNee, W., 1998. Ultrafine (nanometer) particle mediated lung injury. Journal of Aerosol Science 29, 553–560.

Donaldson, K., Stone, V., Clouter, A., Renwick, L., MacNee, W., 2001. Ultrafine particles. Occupational and Environmental Medicine 58 (3), 211–216.

Ferin, J., Oberdörster, G., Penney, D.P., Soderholm, S.C., Gelein, R., Piper, H.C., 1990. Increased pulmonary toxicity of ultrafine particles? I. Particle clearance, translocation, morphology. Journal of Aerosol Science 21, 384–387.

Fubini, B., Mollo, L., Giamello, E., 1995. Free radical generation at the solid/liquid interface of iron-containing minerals. Free Radical Research 23, 593–614.

Gilmour, P.S., Brown, D.M., Lindsay, T.G., Beswick, P.H., MacNee, W., Donaldson, K., 1996. Adverse health effects of PM10 particles: involvement of iron in generation of hydroxyl radical. Occupational Environmental Medicine 53, 817–822.

Hinds, W.C., 1999. Aerosol Technology: Properties, Behavior, and Measurement of Airborne Particles, 2nd Edition. Wiley, New York.

Hitchins, J., Morawska, L., Wolff, R., Gilbert, D., 2000. Concentrations of submicrometer particles from vehicle emissions near a major road. Atmospheric Environment 34, 51–59.

IARC, 1989. IARC Monographs on the Evaluation of Carcinogenic Risks to Human: Diesel and Gasoline Engine Exhausts and Some Nitroarenes, Vol. 46. IARC, Lyon, pp. 35–36.

Janssen, N., Vanmansom, D., Vanderjagt, K., Harssema, H., Hoek, G., 1997. Mass concentration and elemental composition of airborne particulate matter at street and background locations. Atmospheric Environment 31, 1185–1193.

Kittelson, D.B., 1998. Engines and nanoparticles: a review. Journal of Aerosol Science 29, 575–588.

Kittelson, D.B., Watts, W.F., Johnson, J.P., 2001. Fine particle (Nanoparticle) emissions on Minnesota Highways. Fical Report, Minnesota Department of Transportation.

Kuhler, M., Krafft, J., Bess, H., Heeren, U., Schurmann, D., 1994. Comparison between measured and calculated concentrations of nitrogen oxides and ozone in the vicinity of a motorway. Science of the Total Environment 147, 387–394.

Morawska, L., Bofinger, N.D., Kocis, L., Nwankwoala, A., 1998a. Submicrometer and super micromster particles from diesel vehicle emissions. Environmental Science and Technology 32, 2033–2042.

Morawska, L., Thomas, S., Bofinger, N.D., Wainwright, D., Neale, D., 1998b. Comprehensive characterization of aerosols in a subtropical urban atmosphere: particle size distribution and correlation with gaseous pollutants. Atmospheric Environment 32, 2461–2478.

Morawska, L., Thomas, S., Gilbert, D., Greenaway, C., Rijnders, E., 1999. A study of the horizontal and vertical profile of submicrometer particles in relation to a busy road. Atmospheric Environment 33, 1261–1274.

Oberdörster, G., 1996. Significance of particle parameters in the evaluation of exposure-dose-response relationships of inhaled particles. Particulate Science and Technology 14 (2), 135–151.

Oberdörster, G., 2001. Pulmonary effects of inhaled ultrafine particles. International Archives of Occupational and Environmental Health 74 (1), 1–8.

Osunsanya, T., Prescott, G., Seaton, A., 2001. Acute respiratory effects of particles: mass or number? Occupational and Environmental Medicine 58 (3), 154–159.

Penttinen, P., Timonen, K.L., Tittanen, P., Mirme, A., Ruuskanen, J., Pekkanen, J., 2001. Ultrafine particles in urban air and respiratory health among adult asthmatics. European Respiratory Journal 17 (2), 428–435.

Peters, A., Wichmann, H.E., Tuch, T., Heinrich, J., Heyder, J., 1997. Respiratory effects are associated with the number of ultrafine particles. American Journal of Respiratory and Critical Care Medicine 155 (4), 1376–1383.

Pope, C.A., Thun, M.J., Namboodiri, M.M., Dockery, D.W., Evans, J.S., Speizer, F.E., Heath Jr., C.W., 1995. American Journal of Respiratory and Critical Care Medicine 151, 669.

Rickeard, D.J., Bateman, J.R., Kwon, Y.K., McAughey, J.J., Dickens, C.J., 1996. Exhaust particle size distribution: vehicle and fuel influences in light duty vehicles. SAE paper No. 961986.

Risovoki, Z.D., Morawska, L., Bofinger, N.D., Hitchins, J., 1998. Submicrometer and supermicrometer particles from spark ignition vehicles. Environmental Science and Technology 32, 3845–3852.

Roorda-Knape, M., Janssen, N., De Harthog, J., Van Vliet, P., Harssema, H., Brunekreef, B., 1998a. Air pollution from traffic in city districts near major motorways. Atmospheric Environment 32, 1921–1930.

Roorda-Knape, M., Janssen, N., De Harthog, J., VanVliet, P., Harssema, H., Brunekreef, B., 1998b. Air pollution from traffic in city districts near major motorways. Atmospheric Environment 32, 1921–1930.

Schauer, J.J., Rogge, W.F., Hildemann, L.M., Mazurek, M.A., Cass, G.R., Simoneit, B.R.T., 1996. Source apportionment of airborne particulate matter using organic compounds as tracers. Atmospheric Environment 30, 3837–3855.

Schwartz, J., 1991. Air Pollution and daily mortality in Philadelphia. Presented at the 1991 Meeting of the American Lung Association, Anaheim, CA.

Shi, J.P., Khan, A.A., Harrison, R.M., 1999. Measurements of ultrafine particle concentration and size distribution in the urban atmosphere. Science of the Total Environment 235, 51–64.

Shi, J.P., Evans, D.E., Khan, A.A., Harrison, R.M., 2001. Sources and concentration of nanoparticles (<10 nm diameter) in the urban atmosphere. Atmospheric Environment 35, 1193–1202.

SigmaPlot 2000 for Window Version 6.0 manual, SPSS Inc. 2000.

GL14 Continued

US Environmental Protection Agency, 2000. Office of transportation and air quality, EPA420-B-00-001.

Vedal, S., 1997. Ambient particles and health: lines that divide. Journal of the Air and Waste Management Association 47, 551–581.

Williams, I.D., McCrae, I.S., 1995. Road traffic nuisance in residential and commercial area. Science of the Total Environment 169, 75–82.

Wrobel, A., Rokita, E., Maenhaut, W., 2000. Transport of traffic-related aerosols in urban area. Science of the Total Environment 257, 199–211.

Zhu, Y., Hinds, W.C., Kim, S., Sioutas, C., 2002. Concentration and size distribution of ultrafine particles near a major highway. Journal of the Air and Waste Management Association, accepted for publication.

GL14 Continued

Atmospheric Environment 43 (2009) 2541–2549

Contents lists available at ScienceDirect

Atmospheric Environment

journal homepage: www.elsevier.com/locate/atmosenv

A wide area of air pollutant impact downwind of a freeway during pre-sunrise hours

Shishan Hu [a,b], Scott Fruin [c], Kathleen Kozawa [a,d], Steve Mara [d], Suzanne E. Paulson [b], Arthur M. Winer [a,*]

[a] Environmental Health Sciences Department, School of Public Health, 650 Charles E. Young Drive South, University of California, Los Angeles, CA 90095-1772, USA
[b] Department of Atmospheric and Oceanic Sciences, 405 Hilgard Ave., University of California, Los Angeles, CA 90095-1565, USA
[c] Preventive Medicine, Environmental Health Division, Keck School of Medicine, University of Southern California, 1540 Alcazar Street CHP-236 Los Angeles, CA 90032, USA
[d] California Air Resources Board, Research Division, 1001 I Street, Sacramento, CA 95814, Air Resources Board, Sacramento, CA 95812, USA

ARTICLE INFO

Article history:
Received 10 October 2008
Received in revised form
13 February 2009
Accepted 13 February 2009

Keywords:
Vehicle-related air pollutants
Ultrafine particles
Mobile platform
Roadway
Exposure assessment

ABSTRACT

We have observed a wide area of air pollutant impact downwind of a freeway during pre-sunrise hours in both winter and summer seasons. In contrast, previous studies have shown much sharper air pollutant gradients downwind of freeways, with levels above background concentrations extending only 300 m downwind of roadways during the day and up to 500 m at night. In this study, real-time air pollutant concentrations were measured along a 3600 m transect normal to an elevated freeway 1–2 h before sunrise using an electric vehicle mobile platform equipped with fast-response instruments. In winter pre-sunrise hours, the peak ultrafine particle (UFP) concentration ($\sim$95 000 cm^{-3}) occurred immediately downwind of the freeway. However, downwind UFP concentrations as high as $\sim$40 000 cm^{-3} extended at least 1200 m from the freeway, and did not reach background levels ($\sim$15 000 cm^{-3}) until a distance of about 2600 m. UFP concentrations were also elevated over background levels up to 500 m upwind of the freeway. Other pollutants, such as NO and particle-bound polycyclic aromatic hydrocarbons, exhibited similar long-distance downwind concentration gradients. In contrast, air pollutant concentrations measured on the same route after sunrise, in the morning and afternoon, exhibited the typical daytime downwind decrease to background levels within $\sim$300 m as found in earlier studies. Although pre-sunrise traffic volumes on the freeway were much lower than daytime congestion peaks, downwind UFP concentrations were significantly higher during pre-sunrise hours than during the daytime. UFP and NO concentrations were also strongly correlated with traffic counts on the freeway. We associate these elevated pre-sunrise concentrations over a wide area with a nocturnal surface temperature inversion, low wind speeds, and high relative humidity. Observation of such wide air pollutant impact area downwind of a major roadway prior to sunrise has important exposure assessment implications since it demonstrates extensive roadway impacts on residential areas during pre-sunrise hours, when most people are at home.

1. Introduction

Air quality in the vicinity of roadways can be seriously impacted by emissions from heavy traffic flows. As a result, high concentrations of air pollutants are frequently present in the vicinity of roadways and may result in adverse health effects. These include increased risk of reduced lung function (Brunekreef et al., 1997), cancer (Knox and Gilman, 1997; Pearson et al., 2000), adverse respiratory symptoms (Van Vliet et al., 1997; Venn et al., 2001; Janssen et al., 2003), asthma (Lin et al., 2002; McConnell et al., 2006), and mortality (Hoek et al., 2002).

Previous studies have shown elevated vehicle-related air pollutant concentrations and gradients downwind of roadways during daytime. Hitchins et al. (2000) measured concentrations of fine and ultrafine particles (UFP) at a distance of 15–375 m from a major roadway during the daytime. They found concentrations decayed to about half of the peak value (at the closest point to the roadway) at approximately 100–150 m from the roadway on the normal downwind side. Particle concentrations were not affected by the roadway at a distance farther than 15 m on the normal upwind side, indicating a sharp gradient of fine and ultrafine particles. Similar studies were conducted by Zhu et al. (2002a,b), who measured ultrafine particles, CO, and black carbon (BC) on the upwind (200 m) and downwind (300 m) sides of a freeway in Los Angeles during the daytime. Peak concentrations were observed immediately adjacent to the freeway, with concentrations of air pollutants returning to upwind background levels about 300 m downwind of the freeway.

* Corresponding author. Tel.: +1 (310)206 1278; fax: +1 (310)206 3358.
E-mail addresses: hushishan@ucla.edu (S. Hu), fruin@usc.edu (S. Fruin), kkozawa@arb.ca.gov (K. Kozawa), smara@arb.ca.gov (S. Mara), paulson@atmos.ucla.edu (S.E. Paulson), atmwiner@ucla.edu (A.M. Winer).

1352-2310/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.atmosenv.2009.02.033

GL14 Continued

The few near-roadway studies conducted at night indicated larger areas of impact than during daytime. UFP concentrations at night were reported by Zhu et al. (2006), who conducted measurements upwind (300 m) and downwind (500 m) of a freeway from 22:30 to 04:00. Although traffic volumes were much lower at night (about 25% of peak) particle number concentrations were about 80% of the daytime peak 30 m downwind of the freeway, with UFP concentrations of $\sim$50 000 cm^{-3} about 500 m downwind of I-405, a major Los Angeles freeway during the night. Fruin and Isakov (2006) measured UFP concentrations in Sacramento, California, near the I-50 freeway between 23:00 and 01:00 and found 30–80% of maximum centerline concentrations (measured on a freeway overpass) 800 m downwind.

In the present study, the use of a full-size, motorized mobile platform (MP) allowed more pollutants to be measured than previous nighttime studies and with improved spatial and temporal resolution. While traveling at normal vehicle speeds, an instrumented mobile platform allows measurements over greater distances and in shorter times (Bukowiecki et al., 2002a,b, 2003; Canagaratna et al., 2004; Kittelson et al., 2004a,b; Khlystov and Ma, 2006; Kolb et al., 2004; Pirjola et al., 2004, 2006; Unal et al., 2004; Weijers et al., 2004; Westerdahl et al., 2005; Yao et al., 2005; Isakov et al., 2007; Baldauf et al., 2008; Fruin et al., 2008). However, to date, such studies have focused almost entirely on daytime and evening periods.

In the present study, air pollutant concentrations were measured over a wide area on the south and north sides of the I-10 freeway in west Los Angeles, California, 1–2 h before sunrise in the winter and summer seasons of 2008 using an electric vehicle mobile platform equipped with fast-response instruments. We observed a much wider area of impact downwind of the freeway than reported in previous daytime and evening studies, consistent with low wind speed, absence of turbulent mixing, and nocturnal radiation inversions. Our pre-sunrise results were also strikingly different from those we observed for the same route during the daytime. Our observation of a wide area of impact during pre-sunrise hours, up to about 600 m upwind and 2000 m downwind, has significant implications for exposures in residential neighborhoods adjacent to major roadways.

2. Methods

2.1. Mobile platform and data collection

A Toyota RAV4 sub-SUV electric vehicle served as the mobile platform, with self-pollution eliminated by the non-polluting nature of the vehicle. Table 1 shows a complete list of sampling instruments and equipment installed on the mobile platform. The time resolution for most instruments ranged from 5 to 10 s except the Aethalometer, which had 1 min time resolution. The instrument power supply and sampling manifold were similar to that described by Westerdahl et al. (2005).

Calibration checks and flow checks were conducted on a bi-monthly and daily basis, respectively, as described in Kozawa et al. (2009). For calibrations, a standard gas containing a mix of NO and CO was diluted using an Environics 9100 Multi-Gas Calibrator and Teledyne API Zero Air System (Model 701) to calibrate the CO and NO_y/NO$_x$ analyzers. CO_2 was calibrated with zero air and span gas cylinders from Thermo Systems Inc. A DryCal DC-lite flow meter, with a flow range of 100 ml min^{-1} to 7 L min^{-1} and an accuracy of ±1%, was used to check the flows of each instrument.

Table 1
Monitoring instruments on the mobile platform.

Instrument	Measurement Parameter	Time Resolution
TSI Portable CPC, Model 3007	UFP Count (10 nm–1um)	10 s
TSI EMPS, Model 3091	UFP Size (5.6–560 nm)	10 s
TSI DustTrak, Model 8520	PM2.5 Mass	5 s
Magee Scientific Aethalometer	Black Carbon	1 min
EcoChem PAS 2000	Particle Bound PAH	5 s
Teledyne API Model 300E	CO	20 s
LI-COR, Model LI-820	CO2	10 s
Teledyne-API Model 200E	NO_y, NO, NO_2	20 s
Vaisala Sonic Anemometer and Temperature/RH Sensor	Local Wind Speed and Direction, Temperature, Relative Humidity (RH)	1s
Stalker LIDAR and Video Digital System	Traffic Documentation, Distance and Relative Speed	1s

2.2. Route

For pre-sunrise measurements, the mobile platform was driven on a fixed route over three days in the winter season and two days in the summer season of 2008. The route covered a total length of about 3600 m approximately perpendicular to the I-10 freeway in Santa Monica, California (Fig. 1). The solid line in Fig. 1 shows the section of the route over which the mobile platform traveled about 8–10 times during each monitoring period, reaching about 1200 m south of the freeway. The dashed line shows the extended section of the route, over which the mobile platform traveled 2–4 times during each monitoring period, reaching about 2600 m south of the freeway. The pre-sunrise route crossed a number of local surface streets; these are shown in Fig. 1 together with their normal distances to the freeway as measured from Google Map. The route was selected because it passed under the I-10 freeway, and because there was little traffic flow on the route itself or on the perpendicular surface streets (e.g. Olympic Blvd., Pico Blvd. etc.) during pre-sunrise hours. Hence, the majority of measurements were not significantly affected by local surface street traffic. The route also passed through a dense residential neighborhood where the elevated air pollutant concentrations have significant exposure implications.

During sampling, the mobile platform was intentionally stopped to avoid localized impacts from individual vehicles whenever necessary. During data reduction, pollutant concentration spikes, if verified from videotape to be caused by a nearby vehicle, were excluded from the analysis.

2.3. Real-time traffic flow

Traffic flows were collected or measured on the I-10 freeway, the pre-sunrise route itself, and the major surface streets transecting the pre-sunrise route. Real-time traffic flow on the freeway was obtained from the Freeway Performance Measurement System (PeMS) provided by the UC Berkeley Institute of Transportation. Sensors were located at the Dorchester Station, about 300 m from the intersection of the pre-sunrise route and the freeway. Since there were no on-ramps or exits between the Dorchester Station and our route, the PeMS data accurately represented the traffic flow on the I-10 freeway where our route passed under the freeway. Traffic flow on the pre-sunrise route itself was monitored and recorded by a Stalker Vision Digital System on the mobile platform. The recorded videos were replayed and vehicles on the pre-sunrise

GL14 Continued

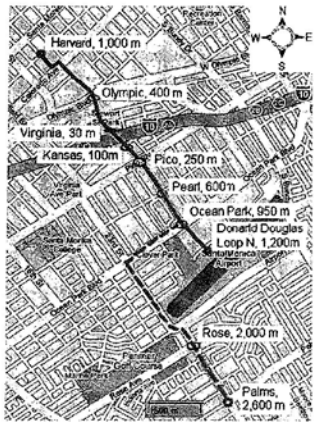


Fig. 1. Pre-sunrise route. The solid line indicates the route 1000 m and 1200 m north and south of the I-10 freeway, respectively. The dashed line indicates the route extended to 2600 m south of the I-10 freeway. Mobile platform measurements on this route were continuous; circles indicate location of cross streets, not fixed site monitoring.

route were manually counted. Traffic flows on the major cross streets (e.g. Olympic Blvd., Pico Blvd., and Ocean Park Blvd.) were manually counted during the winter season on a weekday at times similar to when the pre-sunrise measurements were conducted.

2.4. Data analysis and selection of key pollutants

Data were adjusted for the varying response times of the instruments on the mobile platform to synchronize the measurements. NO_x, CO, CO_2, and particulate data (UFP, BC, and PM2.5 mass) were synchronized with particle-bound polycyclic aromatic hydrocarbon (PB-PAH) data measured by the PAS instrument, which had the fastest response time. NO, UFP, and PB-PAH were selected in the present study for detailed spatial analysis because of their rapid and large variation on and near roadways. The overall response time for the PAS instrument was determined by comparing the time of signal peaks in the PB-PAH time-series to the corresponding time of acceleration of a vehicle in front of our mobile platform (as recorded on videotape). This time difference was less than 10–15 s and includes the transport time (typically a few seconds) for the plume from the emitting vehicle to reach the inlet of the sampling duct of the mobile platform. Given the short response times of our instruments and our driving speeds of 5–15 MPH, the spatial resolution of our mobile platform measurements was typically in the range of 25–75 m, with the finer spatial resolution (~25 m) near the edges of the freeway where we drove more slowly.

Measurements were made continuously over the entire route, not at fixed stationary sites. The measured real-time concentrations of UFP, PB-PAH, and NO along the pre-sunrise route were averaged for each intersection using a few data points measured at and immediately adjacent to the intersection. Although the peak air pollutant concentration always occurred downwind of the I-10 freeway, its value changed with time due to changing traffic volumes on the I-10 freeway and varying meteorological conditions, so peak pollutant concentrations were used to calculate normalized relative pollutant concentrations. For example, in the winter season, the measured averaged peak UFP concentration was about 95 000 cm^{-3}, but the instantaneous peak values varied in the range of 62 000–135 000 cm^{-3} (four to nine times the background concentrations).

3. Results and discussion

3.1. Meteorological data

Meteorological conditions, including atmospheric stability, temperature, relative humidity, wind speed and wind direction, play an important role in determining air pollutant concentrations and gradients along and downwind of roadways. During each run, the mobile platform was periodically stopped at locations along the pre-sunrise route to obtain wind data from on-board instruments (Table 2). These data were compared with the measurements from the Santa Monica Airport (SMA) located about 1500 m downwind of the I-10 freeway and in the immediate vicinity of the route. Both the averaged wind speeds measured by the mobile platform and by the SMA were quite low during pre-sunrise hours, in a range of 0–1.0 m s^{-1} and the averaged difference between the two measurements was about 0.3 m s^{-1}. Temperature and relative humidity were obtained from SMA data.

Fig. 2 shows the wind roses and vector-averaged wind orientation for five days, March 7, 12, 18, June 30, and July 2, from data collected by instruments on the mobile platform. Wind speeds were low during the pre-sunrise hours, with monitoring period averages ranging from 0.0 to 1.0 m s^{-1}. The averaged wind directions measured by the mobile platform indicated a predominant direction of N/NE/NW during the pre-sunrise runs, which agreed reasonably well with airport wind direction data. For this predominant wind direction, the north side of the I-10 freeway was upwind; the south side downwind. Although having a predominant direction from north, the wind was not completely perpendicular to the I-10 freeway. Hence, the distances pollutants traveled from the freeway to various locations along the route, including the major cross-surface streets, were generally longer than indicated by distances shown in Fig. 1. For example, the straight perpendicular distance of Ocean Park Blvd. to the I-10 freeway is ~950 m, whereas for the averaged wind direction of 25° for the pre-sunrise run, the distance pollutants traveled was ~1050 m. However, due to the variability of meteorological conditions, the perpendicular distances were used to indicate impact distances in the present study.

While detailed thermal structure data for the lowest layers of the atmosphere in the area of our pre-sunrise route were not available, the available data indicate the days sampled had stable (i.e., vertical) temperature profiles or strong nocturnal radiation inversions in the hours before sunrise. Data recorded at the Santa Monica Airport indicated the nights on which sampling took place were clear up to at least 3000 m, and had either offshore flow or a weak land breeze, also consistent with clear skies; clear skies are conducive to the formation of nocturnal surface inversions due to enhanced radiative heat loss in the infrared. Data collected by the

GL14 Continued

Table 2
Meteorological conditions during pre-sunrise runs (2008).

Date	Measurement period	Sunrise	Atmospheric Stability from LAX Profiler data	Wind Speed[a] (m s^{-1})		Wind Direction[a] (°)		Temperature (°C)	Relative Humidity (%)
				MP	SMA	MP	SMA	SMA	SMA
March 7	6:20–7:50[b]	7:14[b]	N.A.[c]	0.6	1.0	12	5	11	76
March 12	6:00–7:30	7:07	Surface inversion to 250–300 m	1.8	1.0	53	20	13	66
March 18	6:10–7:20	6:59	Surface inversion to 160 m	0.4	1.0	6	45	9	61
June 30	4:00–6:30	5:45	Stable to 190 m, inversion above	0.7	0.0	288	0	17	87
July 2	4:30–6:45	5:45	Stable to 260 m, inversion above	0.7	1.0	315	340	17	84

[a] Averaged values for the measured period.
[b] Time corrected to Pacific Day Light Time (PDT); change from PST to PDT occurred on March, 9, 2008.
[c] Profiler came online the following evening. The following night (3/8) experienced a surface inversion for the entire night.

South Coast Air Quality Management District (SCAQMD) at the Los Angeles Airport (LAX), ~8 km south of pre-sunrise route, were also consistent with an inversion or stable conditions at the surface. On 3/10 and 3/18, the data showed temperature inversions from the lower edge of the measurements at 130 m up to 190 m or more, respectively. On 6/30 and 7/2, the profiles were stable from 130 to 190 or 260 m, respectively, with capping inversion layers above. Wind speeds during the pre-sunrise hours were too low to create

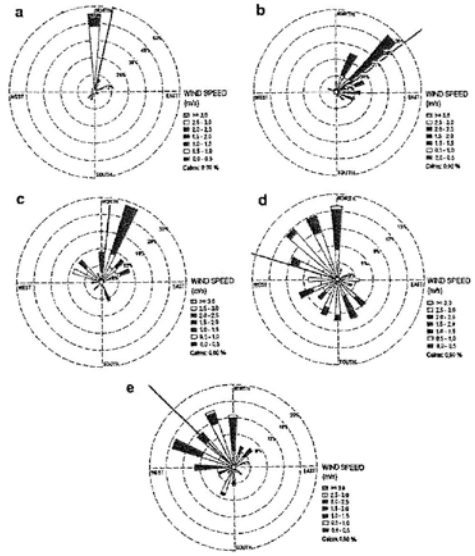


Fig. 2. Wind roses for pre-sunrise sampling hours. (a) March 7; (b) March 12; (c) March 18; (d) June 30; (e) July 2. The thin line in each wind rose indicates vector-averaged wind orientation.

GL14 Continued

appreciable vertical mixing in the presence of these temperature profiles, and the shallow mixed layer was likely thinner in March than in June/July.

3.2. Observation of a wide impact area downwind of the freeway during pre-sunrise hours

As shown in Fig. 3, a wide impact area of elevated UFP concentrations, up to 2000 m downwind and 600 m upwind of the I-10 freeway, was observed during the pre-sunrise hours on the monitoring days in the two seasons. In this wide impact area, elevated UFP concentration extended beyond Donald Douglas Loop N located on the south side and 1200 m downwind of the freeway (Fig. 3). Here, 1200 m downwind, the average UFP concentrations during the winter sampling hours, typically 06:00–07:30, were as high as ~40 000 cm^{-3}. Only at a downwind distance of about 2600 m (Palms Blvd.), did the UFP concentration drop to ~15 000 cm^{-3}, comparable to the upwind background level.

In the winter season, the peak UFP concentration was approximately 95 000 cm^{-3} a few tens of meters downwind of the freeway. Upwind, the concentration dropped sharply to around 40 000 cm^{-3} 30 m upwind (Virginia Avenue) and returned to background levels of ~15 000 cm^{-3} at ~800 m on the upwind side, creating a moderate upwind gradient north of the I-10 freeway (Fig. 3). Interestingly, the upwind impact distance during the pre-sunrise hours, ~600 m, was far greater than that of ~15 m observed during the day by Hitchins et al. (2000) and also greater than that measured by Zhu et al. (2002b). This may be caused by the occasionally variable wind direction during the pre-sunrise hours for which the nominal upwind side of the I-10 freeway could temporarily become downwind. These occasional impacts on the nominal upwind side of the freeway appear to have had substantial influence on the averaged upwind UFP concentrations due to their otherwise low levels.

As seen in Fig. 3, the UFP concentration also decreased on the downwind side, but much more slowly than on the upwind side. At a downwind distance of about 600 m from the freeway, UFP concentrations during winter were about twice those on the upwind side (50 000 cm^{-3} vs. 22 000 cm^{-3}). Even 950 m downwind, at the intersection of Ocean Park Blvd., the UFP concentration remained as high as 45 000 cm^{-3}, higher than at 30 m upwind. These pronounced differences in gradients of UFP concentrations resulted in strong contrasts between the upwind and downwind sides of the I-10 freeway during pre-sunrise hours (Fig. 3).

As shown in Fig. 4, NO and PB-PAH exhibited concentration gradients similar to UFP along the route during the pre-sunrise hours. Peak concentrations of NO and PB-PAH (on the downwind side) were about 165 ppb and 55 ng m^{-3}, respectively, in the winter season. Upwind, NO and PB-PAH concentrations dropped rapidly to 70 ppb and 30 ng m^{-3}, respectively, at a distance of about 150 m. In contrast, on the downwind side, NO and PB-PAH concentrations of 70 ppb and 30 ng m^{-3}, respectively, extended to a distance of about 1200 m from the freeway (NO and PB-PAH data were unavailable for summer measurement due to instrument problems during the pre-sunrise runs).

Fig. 5 shows normalized UFP concentrations on the two sides of I-10 freeway during the pre-sunrise hours in the winter and summer seasons. UFP concentrations were normalized for each complete run traveled on our route, and then averaged together for all the runs for each season. While there was little or no traffic on our route during the pre-sunrise hours, vehicle counts on the same route during the day were much higher and emissions from these vehicles significantly and frequently affected measurements by the mobile platform. Moreover, the pre-sunrise route was only driven once in the morning after sunrise and once in the afternoon, in contrast to multiple times in the pre-sunrise period. For both of these reasons, comparison between pre-sunrise and morning/afternoon measurements on the pre-sunrise route are not meaningful. Instead, we show normalized data from Zhu et al. (2002b), which were not affected by local traffic, to compare with our pre-sunrise measurements.

As Fig. 5 illustrates, pre-sunrise UFP concentration gradients in the present study exhibited very different behavior than the typical narrow daytime UFP gradients measured by Zhu et al. (2002a,b). In our pre-sunrise measurements, UFP concentrations remained elevated above the background level up to ~600 m upwind of the freeway versus only ~17 m upwind for the Zhu et al. (2002b) daytime measurements. On the downwind side in the Zhu et al. (2002b) measurements, UFP concentrations dropped to about 25% of the peak concentration 300 m downwind of the freeway during the day, but in the present study, in strong contrast, the UFP concentrations remained about 40% of the peak as much as 1200 m downwind of the freeway, and was above background levels out to ~2000 m during the pre-sunrise hours.

To quantify these differences in UFP concentrations an equation of the form $C = a + e^{-bx}$ was used to fit our observed relative UFP concentrations downwind of the I-10 freeway during pre-sunrise hours, as well as the daytime data reported by Zhu et al. (2002b). As seen in Fig. 6, the decay constant is a factor of five higher for the

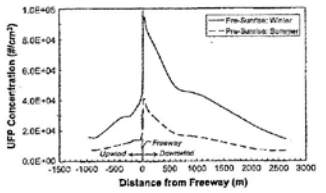


Fig. 3. Ultrafine particle concentrations and gradients along the pre-sunrise route. Positive distances are downwind and negative distances upwind from the I-10 freeway. Data were acquired continuously, up to the edges of the freeway.

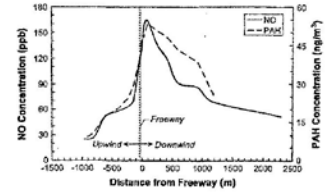


Fig. 4. Average NO and PB-PAH concentrations and gradients, along the pre-sunrise route in the winter season. Positive distances are downwind and negative distances upwind from the I-10 freeway.

GL14 Continued

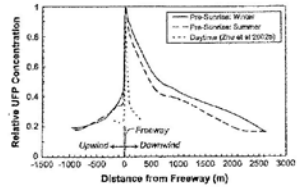


Fig. 5. Relative averaged UFP concentrations and gradients along the pre-sunrise route by season and compared with Zhu et al. (2002b). Positive distances are downwind and negative upwind from the I-10 freeway. Data were acquired continuously for pre-sunrise measurements, up to the edges of the freeway.

daytime vs. the pre-sunrise period, with values of b of 0.0098 and 0.0018, respectively.

Pre-sunrise relative UFP concentrations exhibited similar trends in both winter and summer (Fig. 5). Although UFP concentrations in the summer were about 40% those in the winter (due to lower traffic flows on the I-10 freeway, as discussed below), the similar trends in relative UFP concentration imply similar UFP propagation during the pre-sunrise hours in the two seasons although meteorological conditions were somewhat different.

3.3. Correlation of pollutant concentrations with traffic counts on I-10 freeway

PeMS data showed a similar diurnal traffic pattern on the I-10 freeway on different weekdays during the pre-sunrise hours in both winter and summer (Fig. 7b). Traffic counts on the freeway exhibited an approximately linear increase with the time. However, during 04:00–05:30 (when summer measurements were conducted) traffic counts were lower in summer than in winter. We attribute part of the lower traffic counts in summer to most schools being closed and vacation season in summer, as well as the dramatic increase in gasoline prices between March and July 2008, resulting in a significant overall reduction in vehicle miles traveled. Also, sunrise was about one hour and fifteen minutes earlier in

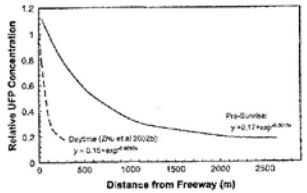


Fig. 6. Exponential fits to the downwind relative UFP concentrations with distance from the I-10 freeway during pre-sunrise hours, compared with fit to daytime data downwind of the I-405 freeway by Zhu et al. (2002b). Data were acquired continuously for pre-sunrise measurements, up to the edges of the freeway.

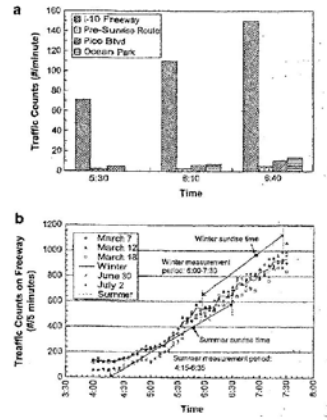


Fig. 7. (a) Comparison of traffic volumes on the I-10 freeway, pre-sunrise route, Palm Blvd., and Ocean Park Blvd. during pre-sunrise hours on a typical weekday; (b) Traffic counts on the I-10 freeway during pre-sunrise measurements; solid line represents averaged count of the three days in the winter season, and dashed line for two days in the summer season. Sunrise times shown here were averaged for each season.

summer (~05:45) than in winter (~07:00), which required an earlier measurement period in summer (~04:15–05:30) compared to winter (~06:00–07:30), and corresponds to much lower overall traffic counts during the pre-sunrise measurement periods in summer.

During the measurement period in winter, traffic counts on the freeway increased from ~530 to ~900 vehicles per 5 min, while in summer counts increased from ~60 to ~620 vehicles per 5 min. Assuming a linear increase of traffic counts with time, the average traffic counts during the pre-sunrise measurements periods, winter versus summer, were ~715 vs. 340 vehicles per 5 min, resulting a ratio of ~2.1. This ratio of seasonal traffic counts compares well with the ratio of the UFP concentrations measured in the winter vs. summer of ~2.2–3.0, depending on distance from the freeway (Fig. 3). It should be noted that the sunrise times during the winter (March) measurements, because they occurred just after the switch to Pacific daylight time (PDT), were close to the latest annual (local) sunrise times, and thus may represent roughly the upper limit for the freeway impact throughout the year.

We attribute the relatively high pollutant concentrations we observed downwind of the I-10 freeway during pre-sunrise hours to emissions of vehicles traveling on the I-10 freeway, combined with strong inhibition of vertical mixing due to stable or inverted temperature profiles near the surface. Fig. 8 shows the UFP and NO concentrations measured at Ocean Park Blvd., ~950 m downwind, vs. the traffic counts on the freeway during the pre-sunrise hours on

GL14 Continued

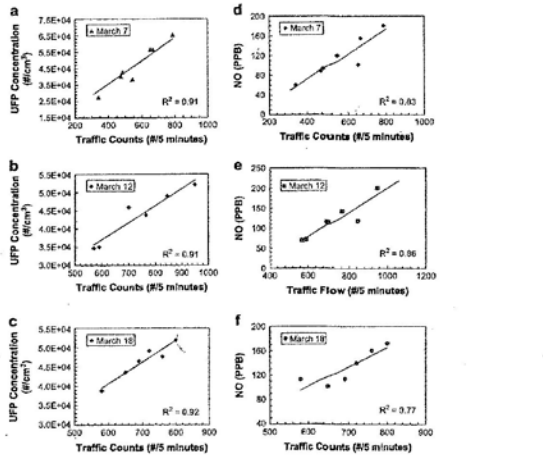


Fig. 8. Linear regressions between UFP and NO concentrations at Ocean Park Blvd. (950 m downwind of I-10 freeway), and traffic counts on the freeway during the pre-sunrise hours in the winter season.

three mornings of the pre-sunrise runs in the winter season. Both the freeway traffic counts (Fig. 7b) and pollutant concentrations increased rapidly during the pre-sunrise hours, and exhibited a strong correlation with each other. For UFP, the values of squared Pearson correlation coefficients (r^2) were above 0.90 and for NO, above 0.77 (nitric oxide data were unavailable for summer measurements due to instrument problems during the pre-sunrise runs). Strong correlations at other distances from the freeway were also found between UFP concentrations and traffic counts on the freeway. For example, the correlation coefficients, r^2 for UFP measured at Pearl St, for three winter sampling days, were above 0.85.

Based on our videotape observations and the traffic counts we conducted on surface streets, as well as the strong correlations presented in Fig. 8, we believe the measured concentrations of air pollutants during the pre-sunrise hours were predominantly determined by the traffic counts on the I-10 freeway, and that the impact of local surface street traffic was minor. Traffic volumes on the pre-sunrise route itself were only about 2% of those on the I-10 freeway at corresponding times. Traffic volumes on the three major surface streets crossing the pre-sunrise route, Ocean Park Blvd., Pico Blvd., (downwind of the freeway), and Olympic Blvd (upwind of the freeway) were also low, only about 8%, 6%, and 6%, respectively, of those on the freeway. Most of this early-morning cross traffic for our measurement route encountered green lights. If the emissions of the occasional vehicles on these surface streets were significant, the pollutant concentrations measured downwind of the streets should have been higher than upwind, but this was not the case; no significant gradients in concentration were observed between the two sides of these streets. Hence, the contribution of emissions from vehicles on the surface streets to our pre-sunrise measurements ranged from minor to insignificant compared to emissions from freeway traffic.

One case in which we find evidence of a minor contribution from non-freeway emissions involves the shallow shoulder in UFP concentrations on Ocean Park Blvd. (~950 m downwind) and shown in Fig. 3. Traffic counts on this major surface street were ~8% of the freeway counts (Fig. 7a), which may have resulted in a small local UFP, NO, and PB-PAH contribution to the measured concentration. A local contribution of ~6% traffic count on Pico Blvd. is not apparent in the measured UFP concentration in Fig. 3, probably due to the closer proximity of Pico Blvd. to the I-10 freeway (~250 m downwind).

Although the mobile platform measurements could be affected by emissions from vehicles occasionally encountered on the pre-sunrise route or cross-surface streets, these encounters typically exhibited only a short, transient spike of elevated concentrations. Furthermore, the overall pre-sunrise concentrations and gradients presented were averaged from 18 to 24 runs in winter and 12–16 runs in summer and for all these reasons were generally not significantly affected by emissions from occasionally encountered nearby vehicles. The Santa Monica Airport (SMA), a small local airport, located south of the pre-sunrise route, had no impact on

GL14 Continued

any of our pre-sunrise measurements since it has severely restricted hours to minimize noise pollution, and was closed during all of our pre-sunrise experiments.

3.4. Size distribution of UFP along pre-sunrise route

The use of a fast mobility particle sizer (FMPS), with its 10 s scans, allowed accurate monitoring of the changing particle size distribution as a function of distance away from the freeway. Fig. 9 shows average UFP size distributions for five downwind and two upwind intersections during the pre-sunrise hours in the winter season, with decreasing particle numbers and increasing sizes as distance downwind increases, until the upwind size distribution was roughly matched at 2600 m. At the downwind intersections up to 1200 m from the freeway, two to four times higher concentrations of ultrafine particles less than 40 nm were observed compared with upwind locations (Fig. 9).

For the intersections nearest the freeway (e.g. Kansas, 100 m downwind, and Pico, 250 m downwind), bi-modal peaks in the size ranges of ~9–12 nm and 16–20 nm were observed. For downwind intersections farther away and for the upwind intersections, UFP peaks observed were typically ~9–12 nm and ~16–20 nm, and 28–35 nm, corresponding to freshly generated UFP and aged particles, respectively. UFP size distributions at a distance of 2600 m downwind (Palms Blvd.) and 1000 m upwind (Harvard St), considered "background" locations, were similar with a dominant mode at 30–60 nm.

In summer, downwind UFP size distributions also had a small mode of 9–12 nm. The persistence of the 9–12 nm peak in UFP concentrations during pre-sunrise hours over a wide area can be attributed to increased condensation of organic vapors and slower rates of conversion to larger particles for the cooler, stable air conditions prior to sunrise during our winter and summer campaigns. These conditions would also promote the more elevated UFP concentrations observed in our pre-sunrise runs compared with daytime runs.

3.5. Pre-sunrise vs. daytime concentrations in present study: exposure implications

Although traffic volumes on the freeway during the pre-sunrise hours were markedly lower than during the daytime (~30–80% of peak congestion traffic volumes), air pollutant concentrations measured prior to sunrise were significantly higher than in the

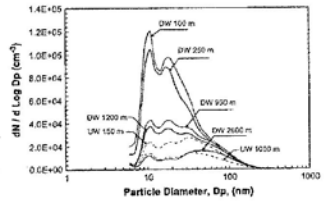


Fig. 9. Size distributions of ultrafine particles measured by a TSI Model 3091 FMPS at upwind (UW) and downwind (DW) intersections during the pre-sunrise hours in the winter season.

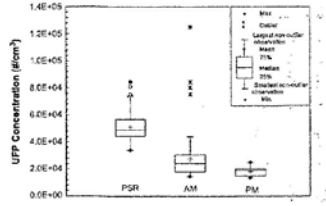


Fig. 10. Comparison of UFP concentrations on Pearl St. (600 m south of I-10 freeway) at different times in winter: pre-sunrise (PSR), morning (AM), and afternoon (PM).

morning or afternoon runs. Fig. 10 shows the UFP concentrations measured at Pearl St., ~600 m south of the freeway, during the pre-sunrise and daytime hours in winter. The median UFP concentrations were 49 000 cm^{-3}, 24 000 cm^{-3}, and 19 000 cm^{-3} for the pre-sunrise, morning, and afternoon, respectively. Clearly, there was sufficient traffic flow on the I-10 freeway combined with the meteorological conditions during pre-sunrise hours to result in elevated concentrations of UFP, NO, and PB-PAH over a wide area of the downwind (up to ~2000 m) and upwind (up to ~600 m) residential neighborhoods. Since the pre-sunrise hours are at a time when most people are in their homes, our observations imply the potential for elevated exposures for many more residents in these neighborhoods, adjacent to freeways; far above the numbers of people that live within the ~300–500 m range reported in earlier daytime and evening studies. Additional measurements in the pre-sunrise period downwind of other major roadways should be conducted to confirm our novel findings.

4. Conclusions

A wide impact area of elevated pollutant concentrations on the downwind (up to ~2000 m) and upwind (up to ~600 m) sides of a freeway was measured during the pre-sunrise hours under typical meteorological conditions characterized by weak winds and a strong radiation inversion. To make these measurements, a mobile platform, equipped with fast-response monitoring instruments, drove along a transect crossing under the I-10 freeway and passing through a large residential neighborhood. On the upwind side of the freeway, air pollutant concentrations dropped quickly, but remained elevated up to ~600 m. On the downwind side, air pollutant concentrations (UFP, PAH, NO) dropped much more slowly and extended far beyond the typical ~300 m distance associated with the return to background pollutant levels observed in previous studies conducted during daytime. For example, elevated ultrafine particle concentration of about 40 000 cm^{-3} extended to ~1200 m downwind of the freeway in the winter season, which was about 40% of the peak UFP concentration adjacent to the freeway.

Although traffic volumes during the pre-sunrise hours were lower than during the day, the UFP concentrations were significantly higher in the pre-sunrise period. We attribute this pre-sunrise phenomenon to strong atmospheric stability, low wind speeds (~0–1 m s^{-1}), low temperatures (~9–13 °C), and high humidities (~61–79%), facilitating longer lifetimes and slower transport of UFP before dilution and dispersion to background levels. Nocturnal inversions are

GL14 Continued

a widespread phenomenon particularly on clear nights, and our results suggest broad areas of elevated pollutants around major roadways are expected to be common in the early-morning hours. The implications of these observations for exposures to vehicle-related pollutants should be further explored.

Acknowledgements

The authors acknowledge support for this study by the California Air Resources Board, Contract No. 04-348. The authors wish to express their appreciation to Drs. Jorn Herner, Ying-Kuang Hsu, and Dane Westerdahl of ARB for their assistance, and Joe Cassmassi and Kelvin Durkee of the SCAQMD for their technical support. We also wish to thank Dr. Richard Turco at UCLA and Dr. Jun Wu at UC, Irvine, as well as Douglas Houston, Albert Chung, Hwajin Kim, Daniel Curtis and Shahir Masri at UCLA, for their contributions to the study. Helpful discussions with James Murakami at UCLA regarding the sources of meteorological data and their interpretation are greatly appreciated.

References

Baldauf, R., Thoma, E., Hays, M., Shores, R., Kinsey, J., Gullett, B., Kimbrough, S., Isakov, V., Long, T., Snow, R., Khlystov, A., Weinstein, J., Chen, F., Seila, R., Olson, D., Gilmour, I., Cho, S., Watkins, N., Rowley, P., Bang, J., 2008. Traffic and meteorological impacts on near-road air quality: summary of methods and trends from the Raleigh near-road study. Journal of the Air and Waste Management Association 58, 865–878.
Brunekreef, B., Janssen, N.A.H., de Hartog, J., Harssema, H., Knape, M., van Vliet, P., 1997. Air pollution from truck traffic and lung function in children living near motorways. Epidemiology 8, 298–303.
Bukowiecki, N., Dommen, J., Prévôt, A.S.H., Richter, R., Weingartner, E., Baltensperger, U.J., 2002a. A mobile pollutant measurement laboratory-measuring gas phase and aerosol ambient concentrations with high spatial and temporal resolution. Atmospheric Environment 36, 5569–5579.
Bukowiecki, N., Kittelson, D.B., Watts, W.F., Burtscher, H., Weingartner, E., Baltensperger, U., 2002b. Real-time characterization of ultrafine and accumulation mode particles in ambient combustion aerosols. Journal of Aerosol Science 33, 1139–1154.
Bukowiecki, N., Dommen, J., Prévôt, A.S.H., Weingartner, E., Baltensperger, U., 2003. Fine and ultrafine particles in the Zürich (Switzerland) area measured with a mobile laboratory. An assessment of the seasonal and regional variation throughout a year. Atmospheric Chemistry and Physical Discussion 3, 2739–2782.
Canagaratna, M.R., Jayne, J.T., Ghertner, D.A., Herndon, S., Shi, Q., Jimenez, J.L., Silva, P.J., Williams, P., Lanni, T., Drewnick, F., Demerjian, K.L., Kolb, C.E., Worsnop, D.R., 2004. Chase studies of particulate emissions from in-use New York City vehicles. Aerosol Science and Technology 38, 555–573.
Fruin, S., Isakov, V., 2006. Ultrafine particle concentrations near freeways at night or early morning under Calm conditions. 25th International Conference of the American Association for Aerosol Research, St. Paul, Minnesota. Abstract 8H19.
Fruin, S., Westerdahl, D., Sax, T., Sioutas, C., Fine, P.M., 2008. Measurements and predictors of on-road ultrafine particle concentrations and associated pollutants in Los Angeles. Atmospheric Environment 42, 207–219.
Hitchins, J., Morawska, L., Wolff, R., Gilbert, D., 2000. Concentrations of submicrometer particles from vehicle emissions near a major road. Atmospheric Environment 34, 51–59.
Hoek, G., Brunekreef, B., Goldbohm, S., Fischer, P., van den Brandt, P.A., 2002. Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. The Lancet 360, 203–1209.
Isakov, V., Touma, S., Khlystov, A., 2007. A method of assessing air toxics concentrations in urban areas using mobile platform measurements. Journal of the Air and Waste Management Association 57, 1286–1295.
Janssen, N.A.H., Brunekreef, B., van Vliet, P., Aarts, F., Meliefste, K., Harssema, H., Fischer, P., 2003. The relationship between air pollution from heavy traffic and allergic sensitization, bronchial hyperresponsiveness, and respiratory symptoms in Dutch school children. Environmental Health Perspectives 111, 1512–1518.
Khlystov, A., Ma, Y., 2006. An on-line instrument for mobile measurement of the spatial variability of hexavalent and trivalent chromium in urban air. Atmospheric Environment 40, 8088–8093.
Kittelson, D.B., Watts, W.F., Johnson, J.P., 2004a. Nanoparticle emissions on Minnesota highways. Atmospheric Environment 38, 9–19.
Kittelson, D.W., Watts, W., Johnson, J., Remerowki, M., Ische, E., Oberdorster, G., Gelein, R., Elder, A., Hopke, P., Kim, E., Zhao, W., Zhou, L., Jeong, C.-H., 2004b. On-road exposure to highway aerosols. I. Aerosol and gas measurements. Inhalation Toxicology 16 (S1), 31–39.
Knox, E.G., Gilman, E.A., 1997. Hazard proximities of childhood cancers in Great Britain from 1953–80. Journal of Epidemiology and Community Health 51, 151–159.
Kolb, C.E., Herndon, S.C., McManus, J.B., Shorter, J.H., Zahniser, M.S., Nelson, D.D., Jayne, J.T., Canagaratna, M.R., Worsnop, D.R., 2004. Mobile laboratory with rapid response instruments for real-time measurements of urban and regional trace gas and particulate distributions and emission source characteristics. Environmental Science and Technology 38, 5694–5703.
Kozawa, K.H., Fruin, S.A., Winer, A.M., 2009. Near-road air pollution impacts of goods movement in communities adjacent to the Ports of Los Angeles and Long Beach. Atmospheric Environment. doi:10.1016/j.atmosenv.2009.02.042.
Lin, S., Munsie, J.P., Hwang, S.-A., Fitzgerald, E., Cayo, M.R., 2002. Childhood asthma hospitalization and residential exposure to state route traffic. Environmental Research 88, 71–81.
McConnell, R., Berhane, K., Yao, L., Jerrett, M., Lurmann, F., Gilliland, F., Kunzli, N., Gauderman, J., Avol, E., Thomas, D., Peters, J., 2006. Traffic, susceptibility, and childhood asthma. Environmental Health Perspectives 114, 766–772.
Pearson, R.L., Watchel, H., Ebi, K.L., 2000. Distance-weighted traffic density in proximity to a home is a risk factor for leukemia and other childhood cancers. Journal of the Air and Waste Management Association 50, 175–180.
Pirjola, L., Parviainen, H., Hussein, T., Valli, A., Hameri, K., Aaalto, P., Virtanen, A., Keskinen, J., Pakkanen, T.A., Makela, T., Hillamo, R.E., 2004. Sniffer - a novel tool for chasing vehicles and measuring traffic pollutants. Atmospheric Environment 38, 3625–3635.
Pirjola, L., Paasonen, P., Pfeiffer, D., Hussein, T., Hameri, K., Koskentalo, T., Virtanen, A., Ronkko, T., Keskinen, J., Pakkanen, T.A., Hillamo, R.E., 2006. Dispersion of particles and trace gases nearby a city highway: mobile laboratory measurements in Finland. Atmospheric Environment 40, 867–879.
Unal, A., Frey, C.H., Rouphail, N.M., 2004. Quantification of highway vehicle emission hot spots based on on-board measurements. Journal of the Air and Waste Management Association 54, 130–140.
Van Vliet, P., Knape, M., de Hartog, J., Janssen, N., Harssema, H., Brunekreef, B., 1997. Motor vehicle exhaust and chronic respiratory symptoms in children living near freeways. Environmental Research 74 (2), 122–132.
Venn, A.J., Lewis, S.A., Cooper, M., Hubbard, R., Britton, J., 2001. Living near a main road and the risk of wheezing illness in children. American Journal of Respiratory Care Medicine 164, 2177–2180.
Weijers, E.P., Khlystov, A.Y., Kos, G.P.A., Erisman, J.W., 2004. Variability of particulate matter concentrations along roads and motorways determined by a moving measurement unit. Atmospheric Environment 38, 2993–3002.
Westerdahl, D., Fruin, S.A., Sax, T., Fine, P.M., Sioutas, C., 2005. Mobile platform measurements of ultrafine particles and associated pollutant concentrations on freeways and residential streets in Los Angeles. Atmospheric Environment 39, 3597–3610.
Yao, X., Lau, N.T., Fang, M., Chan, C., 2005. Real-time observation of the transformation of ultrafine atmospheric particle modes. Aerosol Science and Technology 39, 831–841.
Zhu, Y., Hinds, W.C., Kim, S., Shen, S., Sioutas, C., 2002a. Concentration and size distribution of ultrafine particles near a major highway. Journal of the Air and Waste Management Association 52, 1032–1043.
Zhu, Y., Hinds, W.C., Kim, S., Shen, S., Sioutas, C., 2002b. Study of ultrafine particles near a major highway with heavy-duty diesel traffic. Atmospheric Environment 36, 4323–4335.
Zhu, Y., Kuhn, T., Mayo, P., Hinds, W., 2006. Comparison of daytime and nighttime concentration profiles and size distributions of ultrafine particles near a major highway. Environmental Science and Technology 40, 2531–2536.

GL14 Continued

Circulation Research

American Heart Association. Learn and Live.

Ambient Particulate Pollutants in the Ultrafine Range Promote Early Atherosclerosis and Systemic Oxidative Stress

Jesus A. Araujo, Berenice Barajas, Michael Kleinman, Xuping Wang, Brian J. Bennett, Ke Wei Gong, Mohamad Navab, Jack Harkema, Constantinos Sioutas, Aldons J. Lusis and Andre E. Nel

Circ. Res. 2008;102;589-596; originally published online Jan 17, 2008;
DOI: 10.1161/CIRCRESAHA.107.164970
Circulation Research is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7330. Online ISSN: 1524-4571

GL14 Continued

GL14 Continued

Integrative Physiology

Ambient Particulate Pollutants in the Ultrafine Range Promote Early Atherosclerosis and Systemic Oxidative Stress

Jesus A. Araujo, Berenice Barajas, Michael Kleinman, Xuping Wang, Brian J. Bennett, Ke Wei Gong, Mohamad Navab, Jack Harkema, Constantinos Sioutas, Aldons J. Lusis, Andre E. Nel

Abstract—Air pollution is associated with significant adverse health effects, including increased cardiovascular morbidity and mortality. Exposure to particulate matter with an aerodynamic diameter of <2.5 μm ($PM_{2.5}$) increases ischemic cardiovascular events and promotes atherosclerosis. Moreover, there is increasing evidence that the smallest pollutant particles pose the greatest danger because of their high content of organic chemicals and prooxidative potential. To test this hypothesis, we compared the proatherogenic effects of ambient particles of <0.18 μm (ultrafine particles) with particles of <2.5 μm in genetically susceptible (apolipoprotein E–deficient) mice. These animals were exposed to concentrated ultrafine particles, concentrated particles of <2.5 μm, or filtered air in a mobile animal facility close to a Los Angeles freeway. Ultrafine particle–exposed mice exhibited significantly larger early atherosclerotic lesions than mice exposed to $PM_{2.5}$ or filtered air. Exposure to ultrafine particles also resulted in an inhibition of the antiinflammatory capacity of plasma high-density lipoprotein and greater systemic oxidative stress as evidenced by a significant increase in hepatic malondialdehyde levels and upregulation of Nrf2-regulated antioxidant genes. We conclude that ultrafine particles concentrate the proatherogenic effects of ambient PM and may constitute a significant cardiovascular risk factor. (*Circ Res*. 2008;102:589-596.)

Key Words: air pollution ■ ultrafine particles ■ atherosclerosis ■ oxidative stress ■ HDL

It is increasingly being recognized that exposure to ambient particulate matter (PM) contributes to significant adverse health effects and is a risk factor for the development of ischemic cardiovascular events via exacerbation of atherosclerosis, coronary artery disease, and the triggering of myocardial infarctions.[1] Although this association has been documented for PM with a mean aerodynamic diameter of <10 μm (PM_{10}), there is increasing evidence that smaller particles may pose an even greater health risk. A growing literature indicates that fine particles (FPs) with an average aerodynamic diameter of <2.5 μm ($PM_{2.5}$) exert adverse health effects of greater magnitude. For example, the "Women's Health Initiative study demonstrated a 24% increase in the incidence of cardiovascular events and a 76% increase in cardiovascular mortality for every 10 μg/m³ increase in the annual average $PM_{2.5}$ level.[2] It appears that the smallest particles that exist in the urban environment are the most dangerous.[3] Ambient ultrafine particles (UFPs) that have an aerodynamic diameter of <0.18 μm are by far the most abundant particles by number in urban environments such as Los Angeles. Because these particles are emitted mainly by vehicular emissions and other combustion sources, they contain a high content of redox-cycling organic chemicals that could be released deep into the lungs or could even spill over into the systemic circulation. Thus, UFPs may be particularly relevant from the perspective of cardiovascular injury.[3]

In spite of the epidemiological evidence indicating that ambient PM can promote cardiovascular injury and atherosclerosis, the mechanisms of the cardiovascular injury and proatherogenic effects are not clear. However, experimental studies in susceptible animal models have shed some light on disease pathogenesis. For instance, intratracheal administration of ambient PM_{10} in Watanabe rabbits[4] or long-term exposure of apolipoprotein (apo)E-null mice to $PM_{2.5}$[5,6] enhanced atherosclerotic plaque growth. Moreover, a cross-sectional exposure study in humans showed a 5.9% increase in carotid intima–medial thickness for every 10 μg/m³ rise in $PM_{2.5}$ levels,[7] and a prospective cohort study supported an association between long-term residential exposure to high-traffic levels of $PM_{2.5}$ and coronary atherosclerosis, as assessed by coronary artery calcification scores,[8] demonstrating

Original received September 27, 2007; revision received December 20, 2007; accepted January 3, 2008.

From the Department of Medicine (J.A.A., B.B., X.W., B.J.B., K.W.G., M.N., A.J.L., A.E.N.), David Geffen School of Medicine, and Department of Civil and Environmental Engineering (C.S.), University of Southern California, Los Angeles; Department of Community and Environmental Medicine (M.K.), University of California, Irvine; and Department of Pathobiology and Diagnostic Investigation (J.H.), Michigan State University, East Lansing.

This manuscript was sent to Joseph Loscalzo, Consulting Editor, for review by expert referees, editorial decision, and final disposition.

Correspondence to Andre Nel, MD, PhD, Department of Medicine, David Geffen School of Medicine, 10833 Le Conte Ave, CHS 52-175, Box 951680, Los Angeles, CA 90095. E-mail ANel@mednet.ucla.edu

Circulation Research is available at http://circres.ahajournals.org

DOI: 10.1161/CIRCRESAHA.107.164970

that the proatherogenic effects of PM are clinically relevant.[7,8] Air pollution has also been linked to the triggering of acute coronary ischemic events in humans, including myocardial infarction.[9]

We have demonstrated that ambient PM exerts proinflammatory effects in target cells such as endothelial cells,[10] macrophages,[11] and epithelial cells[12] through the generation of reactive oxygen species (ROS) and oxidative stress.[11,13] These prooxidative effects are mediated, in part, by redox-cycling organic chemicals and transition metals that are present on the particle surface.[11] Ambient PM can synergize with oxidized phospholipids in the induction of a wide array of genes involved in vascular inflammatory processes such as atherosclerosis.[10] Moreover, when comparing concentrated ambient particles (CAPs) of various sizes in the Los Angeles basin, UFPs were shown to have the highest content of redox cycling chemicals and therefore displayed the largest prooxidant potential, both abiotically and biotically.[13] We hypothesized, therefore, that UFPs may concentrate some of the PM proatherogenic effects by promoting prooxidant and proinflammatory effects. We used the particle concentrator technology available in the Southern California Particle Center to evaluate the atherogenic potential of concentrated UFPs versus concentrated $PM_{2.5}$ in apoE-null mice. In addition, we evaluated the effects of particle exposures on the plasma high-density lipoprotein (HDL) antiinflammatory activity as well as markers of systemic oxidative stress. Our data show that UFPs are more proatherogenic, exert the strongest prooxidative effects, and are associated with the largest decrease in HDL protective activity. These data are of considerable significance from a regulatory perspective.

Materials and Methods

Detailed methods about histology, immunohistochemistry, blood chemistry, monocyte chemotactic assays, lipid peroxidation assay, RNA extraction, and real-time RT-PCR can be found in the online data supplement at http://circres.ahajournals.org.

Animals and Diet

The Animal Research Committee at The University of California at Los Angeles (UCLA) approved all animal protocols. ApoE$^{-/-}$ (C57BL/6J background) male mice were obtained from The Jackson Laboratory (Bar Harbor, Me). Animals were brought to the UCLA animal facility at 4 weeks of age. Mice were fed a regular chow diet (NIH-31 modified 6% diet; Harlan Teklad, Madison, Wis). Both water and food were administered ad libitum. Animals were randomly assigned to 3 groups (n=17/group) that were sent to a mobile inhalation toxicology laboratory located 300 meters from the 110 Freeway. This freeway carries a high volume of gasoline and diesel motor vehicle transit, resulting in high levels of $PM_{2.5}$ mass and UFP counts at the exposure site (Table). The mobile research laboratory (AirCARE 1) is owned by Michigan State University.[14] Mice were subjected to CAP exposures starting at 6 weeks of age over a 40-day period. One mouse in the FP group and 2 in the UFP group died during the course of the study. Animals were euthanized 24 to 48 hours after completion of the last CAP exposure, and aortas and various organs were harvested. Between exposures, mice were housed in a Hazelton chamber[15] that was ventilated with air from which 99.9% of the incident particles were removed by a HEPA filter.

CAP Exposures and Chemical Characterization

Whole-body exposures were performed simultaneously in sessions of 5 hours per day, 3 days per week, for a combined total of 75 hours.

Table. Characteristics of Experimental Exposure Protocol of ApoE-Null Mice Fed a Normal Chow Diet

Experimental Parameter	
Groups	FA, FP, UFP
Exposure time (dates)	11/03/2005 to 12/12/2005
Exposure time (hours)	75
Total ambient particle no. (particles/cm³)	$3.42 (\pm 3.96) \times 10^4$
No. concentration in FA chamber (particles/cm³)	<5000
No. concentration in FP chamber (particles/cm³)	$4.56 (\pm 1.06) \times 10^5$
Calculated UFP no. concentration in the FP chamber (particles/cm³)	$3.88 (\pm 1.06) \times 10^5$
No. concentration in UFP chamber (particles/cm³)	$5.59 (\pm 1.23) \times 10^4$
Ratio of UFP in the FP vs the UFP chamber*	1:1.44
FP chamber particle enrichment factor	13.35 (±1.6)
UFP chamber particle enrichment factor	16.4 (±1.6)
Mass in FP exposure chamber (μg/m³)	433.29
Mass in UFP exposure chamber (μg/m³)	112.61
$PM_{2.5}$ mass in ambient air (μg/m³)	28.78
UFP mass in ambient air (μg/m³)	8.43

FA, FP, and UFP groups were exposed in a mobile laboratory located in downtown Los Angeles. Values shown are means(±SD). *This ratio was obtained by reducing the particle no. in the FP chamber by 15%, which represents the contribution of particles in the 0.18–2.5 μm range. This also translates into an ~2-fold increase in surface area if a spherical particle shape is assumed.

Particle concentrator technology was used to deliver the CAP exposures. Three animal groups were simultaneously exposed to atmospheres containing concentrated particles of <2.5 μm (FPs), particles of <0.18 μm (UFPs), and filtered air (FA). Briefly, ambient air was drawn through an aluminum duct into the VACES (Versatile Aerosol Concentration Enrichment System)[14,15] and delivered to whole-body exposure chambers.[14,15] The FP and UFP aerosol concentrators delivered 0.01- to 2.5-μm and 0.01- to 0.18-μm aerosols, respectively (Table). The FP atmosphere included sub-18 μm particles that were ≈40% fewer particles than in the UFP chamber. Temperature and airflow were controlled to ensure adequate ventilation and minimize buildup of animal-generated dander, ammonia, CO_2, and thermal stress. Mobilization of mice between the Hazelton chamber and the exposures chambers was performed over the shortest time period possible to limit the exposure to ambient air PM in the trailer. CAP number concentrations were measured with a TSI 3022 Condensation Particle Counter, and particle mass concentration was assessed with a DataRAM Model DK-2000.

Particle mass concentration and elemental CAP composition were measured by particle collection on 37-mm Teflon filters (PTFE 2-μm pore, Gelman Science, Ann Arbor, Mich). Concentrations of inorganic ions (sulfate and nitrate), elemental carbon, organic carbon (OC), polycyclic aromatic hydrocarbon (PAH) content, and particle-bound trace elements and metals was performed as previously described.[16–18]

Statistical Analysis

All data were expressed as means ± SEM unless indicated otherwise. Differences between experimental groups were analyzed by 1-way ANOVA with a 1-tailed Fisher protected least-significance difference (PLSD) post hoc analysis test. Differences were considered statistically significant at $P<0.05$.

GL14 Continued

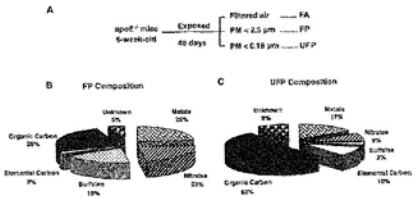


Figure 1. CAP exposures. A, Experimental protocol. Three groups (n=17) of 6-week-old male apoE-null mice were exposed to FA, $PM_{2.5}$, and PM of <0.18 μm (UFPs) for 40 days. B and C, Chemical composition of CAPs. UFP air had a greater content of organic and elemental carbon than FP air. Particle chemical composition of the FP (B) and UFP (C) chambers was performed as described in Materials and Methods.

Results

UFP Exposures Are Enriched in OC Substances Such As PAHs

Six-week-old male apoE-null mice were exposed in a mobile inhalation toxicology laboratory in downtown Los Angeles to CAPs in the size range of <2.5 μm (FP exposures) or <0.18 μm (UFP exposures). Controls consisted of mice exposed to FA (Figure 1A). Animals were simultaneously exposed to UFPs, FPs, and FA for a total of 75 hours over a 40-day time period while being kept on a chow diet. The atmospheric conditions and particle characteristics in the FP and UFP chambers are summarized in the Table. Because the FP atmosphere included particles of <0.18 μm (UFPs) that accounted for up to 85% of the total particle number, the actual number of these sub-0.18 μm particles was ≈44% greater in the UFP chamber (Table), despite a total UFP mass that was approximately one-quarter of the FP mass. Assuming a roughly spherical shape for the particles, this 44% increase in sub-0.18 μm particle numbers in the UFP chamber translates into an ≈2-fold increase in the particle surface area. This was also accompanied by an ≈2-fold increase in fractional OC content (Figure 1B and 1C), which is theoretically more bioavailable than the smaller organic fraction on FPs (Figure 1B). Thus, the increased particle number, greater surface area, and higher fractional carbon composition could combine to deliver a much higher biological effective dose of the injurious components in the UFP compared with the FP chamber. In fact, measurement of a set of signature PAHs in filter samples that were collected concurrently with the CAP exposures, demonstrated that the PAH content of the UFPs was roughly twice as high as the FP content when corrected for a per mass basis (Figure 2). Although there is no definitive evidence that PAHs are those responsible for adverse cardiovascular effects, we have previously demonstrated that their abundance is a good proxy for the prooxidant potential of PM.[13]

UFP Exposure Promotes Atherosclerosis

Exposure to the UFP atmosphere for 75 hours over a 40-day interval resulted in 55% greater aortic atherosclerotic lesion development (33 011±3741, n=15) as compared with FA controls (21 362±2864, n=14; $P=0.002$) (Figure 3). Exposure to the FP atmosphere resulted in a similar trend but of lesser magnitude ($P=0.1$). Interestingly, UFP mice exhibited a 25% increase in atherosclerotic lesions in comparison with FP mice (26 361±2275, n=16, $P=0.04$), which suggests that the smallest particles are indeed more proatherogenic.

Histological analysis revealed that lesions were predominantly comprised of macrophage infiltration with intracellular lipid accumulation (foam cells) (Figure 4). These cells contributed, on average, >85% of the total lesional area in all the groups (supplemental Table I). UFP-exposed animals developed more extensive as well as thicker atherosclerotic plaques that showed the same relative abundance of macrophages and smooth muscle cells, as determined by MOMA-2 and α-actin immunohistochemical staining (Figure 4 and supplemental Table I).

Exposure to Ambient CAPs Results in Loss of HDL Antiinflammatory Properties

FP but not UFP exposures resulted in a small but significant increase in plasma total cholesterol in comparison to other groups (supplemental Table II). Although all animals displayed similar levels of plasma HDL cholesterol (supplemental Table II), we did observe a change in HDL antiinflammatory properties. This was demonstrated by comparing the antiinflammatory protective capacity of HDL against LDL-

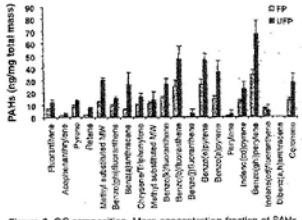


Figure 2. OC composition. Mass concentration fraction of PAHs in the FP (gray) and UFP (black) chambers. Data are shown as nanogram per milligram of PM mass and represent the average of composition analysis performed on filter samples collected for 2 experiments. PAH analysis was performed by means of gas chromatography–mass spectroscopy as described.[16–18]

GL14 Continued

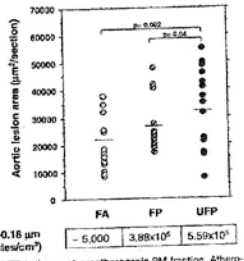


Figure 3. UFP is the most proatherogenic PM fraction. Atherosclerotic lesions were quantitatively analyzed in serial aortic root sections and stained with oil red O. Lesional area was scored as square micrometer per section, averaged ≥25 sections per animal. Group averages are indicated by straight horizontal bars. One FA mouse was an obvious outlier in its group and removed from the atherosclerotic lesion analysis. However, its inclusion did not modify the overall significance. FA mice are represented by dotted circles (n=14), FPs by stripped circles (n=16), and UFPs by filled circles (n=15).

induced chemotaxis (Figure 5). Plasma HDL from both FP and UFP animals exhibited significantly less protective effect than HDL from the FA group (Figure 5). Moreover, the antiinflammatory effect of HDL from the UFP group was significantly decreased compared with the FP group. These results are in good agreement with the extent of vascular lesions in the different animal groups, suggesting that a PM-induced decrease in the HDL antiinflamatory protective capacity could contribute to atherogenesis.

UFP Exposure Leads to the Expression of Systemic Biomarkers of Oxidative Stress and Activation of the Unfolded Protein Response

One of the major mechanistic hypotheses regarding PM injury is the ability of the particles to induce ROS production and oxidative stress. To probe for the presence of oxidative

Figure 5. PM exposure leads to a loss of HDL antiinflammatory properties. Pooled plasma HDL from FA (n=16), FP (n=16) and UFP mice (n=15) was added to cocultures of human artery wall cells in the presence of standard (Std) human LDL, as described in Materials and Methods. Values are expressed as means± SEM of the number of migrated monocytes in 9 fields. Statistical analysis was performed by 1-way ANOVA (Fisher PLSD).

stress, we explored whether CAP exposure could result in lipid peroxidation in the liver. We observed statistically significant increases in the hepatic malondialdehyde (MDA) levels in the UFP compared with the FA group ($P=0.02$) (Figure 6). FP mice also demonstrated increases in lipid peroxidation compared with the FA group ($P=0.03$). These data suggest that CAP exposure leads to systemic oxidative stress.

We also explored whether differences in lipid peroxidation were accompanied by phase II antioxidant responses that are mediated via the p45-NFE2–related transcription factor 2, Nrf2.[11] This constitutes one of the most sensitive oxidative stress effects that can be traced to prooxidative PM in vitro and in vivo.[11,20] UFP mice exhibited a significant increase in the expression of Nrf2 as well as genes that are secondarily regulated by this transcription factor (Figure 7). Indeed, UFP mice displayed Nrf2 mRNA levels that were 68% greater than FA and FP mice ($P=0.01$). Likewise, as compared with the FA group, UFP mice displayed significantly greater levels of catalase (3.7-fold), glutathione *S*-transferase Ya (5.3-fold), NAD(P)H-quinone oxidoreductase 1 (1.8-fold), and superoxide dismutase 2 (1.4-fold) (Figure 7). Interestingly, increased tissue oxidative stress was also accompanied by the activation

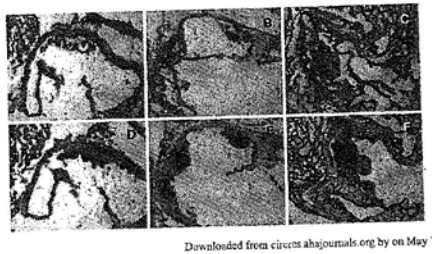


Figure 4. Representative histological photomicrographs. A through C, Oil red O staining for neutral lipids in representative aortic root sections of FA (A), FP (B), and UFP (C) mice. D through F, MOMA-2 immunohistochemical staining in adjacent aortic root sections to those shown in the top row, corresponding to the same FA (D), FP (E), and UFP (F) mice. Both oil red O and MOMA-2 staining yielded red-stained areas. UFP mice exhibited more extensive atherosclerotic plaques (C and F) than FP (B and E) or FA animals (A and D), all consisting primarily of foam cells and macrophages (fatty streaks). Original magnification, ×100.

GL14 Continued

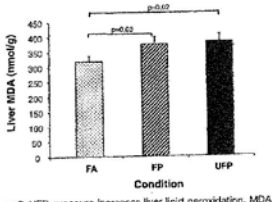


Figure 6. UFP exposure increases liver lipid peroxidation. MDA was assessed in liver homogenates as described in Materials and Methods. Values are expressed as the means±SEM of MDA (nmol/g) in animals from the FA (n=16), FP (n=15), and UFP (n=14) groups. Statistical analysis was performed by 1-way ANOVA (1-tailed Fisher PLSD).

of the unfolded protein response in the liver because the UFP-exposed mice displayed 41% and 37% greater expression of activating transcription factor 4 than FP mice ($P=0.01$) and FA controls ($P=0.02$) (Figure 7).

Discussion

We demonstrate that atherosclerotic plaque formation in apoE-null male mice is enhanced by exposure to sub-0.18 μm particles. Mice exposed to UFPs alone exhibited greater and more advanced lesions compared with FA- or FP-exposed animals. UFP mice also showed a comparatively greater decline in the antiinflammatory capacity of plasma HDL as well as increased phase II enzyme mRNA expression in the liver. These results support the hypothesis that exposure to UFPs may enhance atherosclerosis via the promotion of systemic prooxidant and proinflammatory effects.

Our study significantly extends previous data showing that PM potentiates atherosclerotic lesion development in animals.[4–6] The fact that FP mice displayed a nonstatistically significant trend to develop more atherosclerotic lesions than FA controls could be attributable to the relatively short duration of our exposure (40 days), which stands in contrast to the 5- to 6-month exposure period that was previously used to demonstrate a 45% to 58% increment in atherosclerotic lesion development during $PM_{2.5}$ exposure.[5,6] Of interest, our UFP animals exhibited a similar 55% increment over FA controls despite an exposure duration that was 4 to 5 times shorter, indicating the greater proatherogenic toxicity of sub-0.18 μm particles. This supports the notion that the adverse cardiovascular effects of PM are exaggerated by a small particle size.

A number of injury mechanisms have been proposed to explain the adverse health effects of PM, including its ability to stimulate oxidative stress and inflammation, alter blood clotting, stimulate autonomic nervous system activity, or act as a carrier for endotoxin.[1] A key injury mechanism appears to be the generation of inflammation as a direct consequence of the ability of ambient particles and their adsorbed chemicals to induce ROS and oxidative stress.[21] Oxidative stress

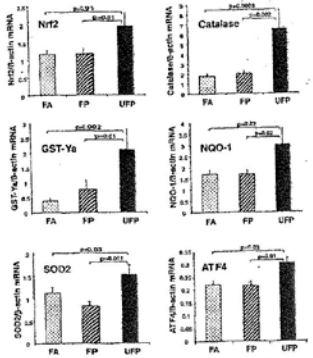


Figure 7. UFP exposure leads to upregulation of antioxidant genes in the liver. mRNA levels for antioxidant genes were determined by quantitative PCR in the livers of chow-fed mice exposed to CAPs for 40 days. Values are expressed as the means±SEM of mRNA levels normalized by β-actin mRNA. Ten samples per group were assayed in duplicate. Statistical analysis was performed by 1-way ANOVA (1-tailed Fisher PLSD; *P<0.05). ATF4 indicates activating transcription factor 4; GST-Ya, glutathione S-transferase Ya; NQO-1, NAD(P)H-quinone oxidoreductase 1; SOD2, superoxide dismutase 2.

initiates proinflammatory signaling cascades, including the Jun kinase and nuclear factor κB cascades[16,22,23] that are relevant to atherogenesis. According to the hierarchical oxidative stress hypothesis, the induction of Nrf2-induced phase II enzyme expression is an integral oxidative stress protective pathway that acts as a sensitive marker for oxidative stress.[24] Indeed, important cytoprotective, antiinflammatory and antioxidant phase II enzymes including catalase, superoxide dismutase 2, glutathione *S*-transferase Ya, and NAD(P)H-quinone oxidoreductase 1 were all significantly upregulated in the liver of UFP mice (Figure 7) and, together with Nrf2 upregulation, suggest the triggering of a Nrf2-driven antioxidant response.

Our results support the notion that the generation of systemic oxidative stress is responsible for the observed vascular effects. Possible explanations for these systemic effects are: First, inhaled particles may release organic chemicals and transition metals from the lung to the systemic circulation. Second, pulmonary inflammation could lead to the release of ROS, cytokines and chemokines to the systemic circulation. Although we did not observe any major increase in inflammatory cells during the performance of bronchoalveolar lavage in these mice, future studies will need to address whether any subtle proinflammatory effects in the lung could play a role. Third, UFPs could gain access to the

GL14 Continued

systemic circulation by directly penetrating the alveolar/capillary barrier.[25] However, this possibility is still controversial. Although reports of the systemic translocation of ^{99m}Tc-labeled ultrafine carbon particles[25] or albumin nanocolloid particles of <80 nm[26] have appeared in the literature, skepticism has been expressed about the stability of the labeling procedures. Moreover, the same has not been demonstrated for ambient air "nanoparticles."

The particles or their chemicals may generate ROS systemically via a number of different pathways, including redox cycling of quinones, metabolism and functionalization of PAHs, activation of leukocyte NADPH oxidase and myeloperoxidase, or interference in 1-electron transfers in the mitochondrial inner membrane.[27] It is also possible that the particles themselves or their chemical components may synergize with oxidized LDL in promoting endothelial cell dysfunction. Indeed, we have shown that ambient PM can synergize with oxidized phospholipids in the induction of a large number of genes in a human microvascular endothelial cell line, many of which belong to antioxidant, proinflammatory, unfolded protein response, or proapoptotic pathways.[10] ROS generation and antioxidant responses constitute a dynamic equilibrium. The greater prooxidant stimulus delivered by the UFPs could be more prone to overwhelm the concomitant generation of a protective antioxidant response. On the other hand, it is interesting that no differences were noted between the FP and UFP exposures in the MDA assay. Although the methodology used is sensitive and specific for the determination of MDA,[28] there are several limitations in this assay in reflecting the degree of lipid peroxidation, as reviewed by Janero et al,[29], such as: (1) MDA yield as a result of lipid peroxidation varies with the nature of the polyunsaturated fatty acids peroxidized (especially its degree of unsaturation) and the peroxidation stimulus; (2) only certain lipid oxidation products decompose to yield MDA; (3) MDA is only one of several (aldehydic) end products of fatty peroxide formation and decomposition; (4) the peroxidation environment influences both the formation of lipid-derived MDA precursors and their decomposition to MDA; (5) MDA itself is a reactive substance that can be oxidatively and metabolically degraded; (6) oxidative injury to nonlipid biomolecules has the potential to generate MDA. Thus, if FP and UFP exposures impacted these factors in a different extent, it may explain a greater degree of lipid peroxidation not reflected by the MDA measurements.

PM-induced systemic inflammation and oxidative stress could also adversely affect lipoprotein function, including interfering in the beneficiary effects of HDL on reverse cholesterol transport[30] and the antiinflammatory[31] effects of this lipoprotein fraction. Indeed, both FP and UFP mice exhibited the development of dysfunctional HDL, which was more severe in the latter group in terms of its proinflammatory potential (Figure 5). Such proinflammatory effects were also supported by the greater expression of activating transcription factor 4 in liver, an unfolded protein response component that we have shown to exert proinflammatory effects in endothelial cells by inducing the expression of interleukin-6, interleukin-8, and monocyte chemotactic protein 1.[32] Likewise, we have also shown that prooxidative diesel exhaust particle chemicals induce an unfolded protein response in bronchial epithelial cells.[33] Changes in HDL function were observed in the absence of changes on HDL quantitative levels. On the other hand, FP exposures did result in greater total cholesterol levels in the FP versus FA mice, whereas UFP levels were unaffected. These higher cholesterol levels in the FP mice may have resulted in narrowing of the differences in atherosclerosis in between FP and UFP mice that otherwise could have been larger than the 23% observed difference. Consistent with our results, it has been reported that the HDL antiinflammatory profile can be hampered by environmental factors such as the exposure to prooxidative chemicals present in cigarette smoke.[34] For example, mice exposed to second-hand smoke develop dysfunctional HDL.[35] A possible mechanism could be interference with paraoxonase and lecithin cholesterol acyltransferase activities by redox-active chemical compounds. In particular, peroxidative PM chemicals may affect critical thiol groups that are responsible for the catalytic activity of paraoxonase, leading to increased susceptibility to atherosclerosis.[36]

The fact that the FP atmosphere contains both UFPs and particles of >0.18 μm makes interpretation of those data complex. However, we have shown that the 25% difference in atherosclerotic lesion scores could be explained by the 44% increase in UFP particle number (Table and Figure 3). Total particle mass was clearly not a determining factor because the FP atmosphere had ≈3.9-fold greater mass than the UFP aerosol. What is likely significant is that UFPs have an ≈2-fold increase in the OC and PAH content on a per mass basis (Figures 1 and 2). It is possible that these prooxidative components could be delivered from a surface area that is twice as big in particles associated with the UFP atmosphere. Although we cannot claim that the PAHs are actually responsible for the lesion development, these organic chemical compounds are a good proxy for the prooxidative potential of UFPs.[13]

How do our experimental atmospheres relate to real life exposures? The particle numbers in our study were 2- to 6-fold higher than the in-vehicle exposures that commuters may encounter while traveling on Los Angeles freeways.[37] It was not logistically feasible to perform detailed dose– and time–response studies; this type of data will be important to obtain in future studies. Although it would clearly be advantageous to know the minimum exposure that is required for proatherogenic effects, previous epidemiological studies have shown that cardiovascular morbidity and mortality increase linearly without a threshold effect.[38,39] Differences in the physiology of genetically susceptible animals and humans also have to be taken into consideration when extrapolating this work to cardiovascular disease in humans.

In conclusion, we demonstrate that UFP exposures have a higher proatherogenic potential than FP exposures. These effects could be linked to a greater propensity of UFPs to generate systemic oxidative stress and to interfere with the antiinflammatory capacity of plasma HDL. Our findings are important in explaining how ambient PM may contribute to daily total and cardiovascular mortality.[40] Although such an association has been established previously for PM_{10} and $PM_{2.5}$,[2,41,42] we demonstrate that UFP exposure could be of

GL14 Continued

GL14 Continued

even greater relevance. Further epidemiological and experimental data collection are required to determine the critical physicochemical and toxicological properties of UFPs in humans.

Acknowledgments

We thank Larry Castellani for the plasma lipoprotein determinations.

Sources of Funding

This work was supported by National Institute of Environmental Health Sciences grant RO1 ES13432 (to A.N.); National Institute of Allergy and Infectious Diseases grant U19 AI070453 (to A.N.); a U.S. Environmental Protection Agency ENERGY STAR Award to the Southern California Particle Center; a Robert Wood Johnson Foundation Harold Amos Medical Faculty Development Program Award (to J.A.A.); and National Heart, Blood, and Lung Institute grant HL30568 (to A.J.L.).

Disclosures

None.

References

1. Nel A. Atmosphere. Air pollution-related illness: effects of particles. *Science*. 2005;308:804–806.
2. Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, Kaufman JD. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med*. 2007;356:447–458.
3. Utell MJ, Frampton MW. Acute health effects of ambient air pollution: the ultrafine particle hypothesis. *J Aerosol Med*. 2000;13:355–359.
4. Suwa T, Hogg JC, Quinlan KB, Ohgami A, Vincent R, van Eeden SF. Particulate air pollution induces progression of atherosclerosis. *J Am Coll Cardiol*. 2002;39:935–942.
5. Sun Q, Wang A, Jin X, Natanzon A, Duquaine D, Brook RD, Aguinaldo JG, Fayad ZA, Fuster V, Lippmann M, Chen LC, Rajagopalan S. Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. *JAMA*. 2005;294:3003–3010.
6. Chen LC, Nadziejko C. Effects of subchronic exposures to concentrated ambient particles (CAPs) in mice. V. CAPs exacerbate aortic plaque development in hyperlipidemic mice. *Inhal Toxicol*. 2005;17:217–224.
7. Künzli N, Jerrett M, Mack WJ, Beckerman B, LaBree L, Gilliland F, Thomas D, Peters J, Hodis HN. Ambient air pollution and atherosclerosis in Los Angeles. *Environ Health Perspect*. 2005;113:201–206.
8. Hoffmann B, Moebus S, Mohlenkamp S, Stang A, Lehmann N, Dragano N, Schmermund A, Memmesheimer M, Mann K, Erbel R, Jockel KH. Residential exposure to traffic is associated with coronary atherosclerosis. *Circulation*. 2007;116:489–496.
9. Peters A, Dockery DW, Muller JE, Mittleman MA. Increased particulate air pollution and the triggering of myocardial infarction. *Circulation*. 2001;103:2810–2815.
10. Gong KW, Zhao W, Li N, Barajas B, Kleinman M, Sioutas C, Horvath S, Lusis AJ, Nel A, Araujo JA. Air-pollutant chemicals and oxidized lipids exhibit genome-wide synergistic effects on endothelial cells. *Genome Biol*. 2007;8:R149.
11. Li N, Alam J, Venkatesan MI, Eiguren-Fernandez A, Schmitz D, Di Stefano E, Slaughter N, Killeen E, Wang X, Huang A, Wang M, Miguel AH, Cho A, Sioutas C, Nel AE. Nrf2 is a key transcription factor that regulates antioxidant defense in macrophages and epithelial cells: protecting against the proinflammatory and oxidizing effects of diesel exhaust chemicals. *J Immunol*. 2004;173:3467–3481.
12. Hiura TS, Kaszubowski MP, Li N, Nel AE. Chemicals in diesel exhaust particles generate reactive oxygen radicals and induce apoptosis in macrophages. *J Immunol*. 1999;163:5582–5591.
13. Li N, Sioutas C, Cho A, Schmitz D, Misra C, Sempf J, Wang M, Oberley T, Froines J, Nel A. Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage. *Environ Health Perspect*. 2003;111:455–460.
14. Harkema JR, Keeler G, Wagner J, Morishita M, Timm E, Hotchkiss J, Marsik F, Dvonch T, Kaminski N, Barr E. Effects of concentrated ambient particles on normal and hypersecretory airways in rats. *Res Rep Health Eff Inst*. 2004;1–68.
15. Brown MG, Moss OR. An inhalation exposure chamber designed for animal handling. *Lab Anim Sci*. 1981;31:717–720.
16. Kim S, Jaques PA, Chang MC, Barone T, Xiong C, Friedlander SK, Sioutas C. Versatile aerosol concentration enrichment system (VACES) for simultaneous in vivo and in vitro evaluation of toxic effects of ultrafine, fine and coarse ambient particles. Part II: field evaluation. *J Aerosol Sci*. 2001;32:1299–1314.
17. Kim S, Jaques PA, Chang MC, Froines JR, Sioutas C. Versatile aerosol concentration enrichment system (VACES) for simultaneous in vivo and in vitro evaluation of toxic effects of ultrafine, fine and coarse ambient particles. Part I: development and laboratory characterization. *J Aerosol Sci*. 2001;32:1281–1297.
18. Kleinman MT, Hamade A, Meacher D, Oldham M, Sioutas C, Chakrabarti B, Stram D, Froines JR, Cho AK. Inhalation of concentrated ambient particulate matter near a heavily trafficked road stimulates antigen-induced airway responses in mice. *J Air Waste Manag Assoc*. 2005;55:1277–1288.
19. Oldham MJ, Phalen RF, Robinson RJ, Kleinman MT. Performance of a portable whole-body mouse exposure system. *Inhal Toxicol*. 2004;16:657–662.
20. Li N, Nel AE. Role of the Nrf2-mediated signaling pathway as a negative regulator of inflammation: implications for the impact of particulate pollutants on asthma. *Antioxid Redox Signal*. 2006;8:88–98.
21. Nel A, Xia T, Madler L, Li N. Toxic potential of materials at the nanolevel. *Science*. 2006;311:622–627.
22. Nel AE, Diaz-Sanchez D, Ng D, Hiura T, Saxon A. Enhancement of allergic inflammation by the interaction between diesel exhaust particles and the immune system. *J Allergy Clin Immunol*. 1998;102:539–554.
23. Gius D, Botero A, Shah S, Curry HA. Intracellular oxidation/reduction status in the regulation of transcription factors NF-kappaB and AP-1. *Toxicol Lett*. 1999;106:93–106.
24. Xiao GG, Wang M, Li N, Loo JA, Nel AE. Use of proteomics to demonstrate a hierarchical oxidative stress response to diesel exhaust particle chemicals in a macrophage cell line. *J Biol Chem*. 2003;278:50781–50790.
25. Nemmar A, Hoet PH, Vanquickenborne B, Dinsdale D, Thomeer M, Hoylaerts MF, Vanbilloen H, Mortelmans L, Nemery B. Passage of inhaled particles into the blood circulation in humans. *Circulation*. 2002;105:411–414.
26. Nemmar A, Vanbilloen H, Hoylaerts MF, Hoet PH, Verbruggen A, Nemery B. Passage of intratracheally instilled ultrafine particles from the lung into the systemic circulation in hamster. *Am J Respir Crit Care Med*. 2001;164:1665–1668.
27. Xia T, Korge P, Weiss JN, Li N, Venkatesen MI, Sioutas C, Nel A. Quinones and aromatic chemical compounds in particulate matter induce mitochondrial dysfunction: implications for ultrafine particle toxicity. *Environ Health Perspect*. 2004;112:1347–1358.
28. Erdelmeier I, Gerard-Monnier D, Yadan JC, Chaudiere J. Reactions of N-methyl-2-phenylindole with malondialdehyde and 4-hydroxyalkenals. Mechanistic aspects of the colorimetric assay of lipid peroxidation. *Chem Res Toxicol*. 1998;11:1184–1194.
29. Janero DR. Malondialdehyde and thiobarbituric acid-reactivity as diagnostic indices of lipid peroxidation and peroxidative tissue injury. *Free Radic Biol Med*. 1990;9:515–540.
30. Zhang Y, Zanotti I, Reilly MP, Glick JM, Rothblat GH, Rader DJ. Overexpression of apolipoprotein A-I promotes reverse transport of cholesterol from macrophages to feces in vivo. *Circulation*. 2003;108:661–663.
31. Barter PJ, Nicholls S, Rye KA, Anantharamaiah GM, Navab M, Fogelman AM. Antiinflammatory properties of HDL. *Circ Res*. 2004;95:764–772.
32. Gargalovic PS, Gharavi NM, Clark MJ, Pagnon J, Yang WP, He A, Truong A, Baruch-Oren T, Berliner JA, Kirchgessner TG, Lusis AJ. The unfolded protein response is an important regulator of inflammatory genes in endothelial cells. *Arterioscler Thromb Vasc Biol*. 2006;26:2490–2496.
33. Jung EJ, Avliyakulov NK, Boontheung P, Loo JA, Nel AE. Pro-oxidative DEP chemicals induce heat shock proteins and an unfolding protein response in a bronchial epithelial cell line as determined by DIGE analysis. *Proteomics*. 2007;7:3906–3918.

34. Ergüder IB, Ergüder T, Ozkan C, Bozkurt N, Soylu K, Devrim E, Durak I. Short-term effects of smoking cessation on blood antioxidant parameters and paraoxonase activity in healthy asymptomatic long-term cigarette smokers. *Inhal Toxicol*. 2006;18:575–579.
35. Navab M, Hama SY, Hough GP, Subbanagounder G, Reddy ST, Fogelman AM. A cell-free assay for detecting HDL that is dysfunctional in preventing the formation of or inactivating oxidized phospholipids. *J Lipid Res*. 2001;42:1308–1317.
36. Gur M, Aslan M, Yildiz A, Demirbag R, Yilmaz R, Selek S, Erel O, Ozdogru I. Paraoxonase and arylesterase activities in coronary artery disease. *Eur J Clin Invest*. 2006;36:779–787.
37. Westerdahl D, Fruin S, Sax T, Fine PM, Sioutas C. Mobile platform measurements of ultrafine particles and associated pollutant concentrations on freeways and residential streets in Los Angeles. *Atmos Environ*. 2005;39:3597–3610.
38. Pope CA 3rd, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, Thurston GD. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA*. 2002;287:1132–1141.
39. Daniels MJ, Dominici F, Samet JM, Zeger SL. Estimating particulate matter-mortality dose-response curves and threshold levels: an analysis of daily time-series for the 20 largest US cities. *Am J Epidemiol*. 2000;152:397–406.
40. Dominici F, McDermott A, Daniels D. Mortality among residents of 90 cities. *Special Report: Revised Analyses of Time-Series Studies of Air Pollution and Health*. Boston, Mass: Health Effects Institute; 2003.
41. Samet JM, Dominici F, Curriero FC, Coursac I, Zeger SL. Fine particulate air pollution and mortality in 20 U.S. cities, 1987–1994. *N Engl J Med*. 2000;343:1742–1749.
42. Pope CA 3rd, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation*. 2004;109:71–77.

GL14 Continued

ONLINE SUPPLEMENT

MATERIALS AND METHODS

Histology and immunohistochemistry

Atherosclerotic lesions in the aortic root were quantitatively analyzed as previously described [1]. Briefly, the upper portion of the heart and proximal aorta was excised and embedded in OCT compound (Tissue-Tek) and frozen [2]. Serial 10-μm-thick cryosections in the aortic root, beginning at the level of the appearance of the aortic valve, were collected for a distance of 500 μm. A total of 25 sections, selected as every other section collected over the entire region, were stained with Oil Red O and counterstained with hematoxylin. The lipid-containing area on each section was determined by using a microscope eyepiece grid and expressed in μm^2 lesional area/section. The mean value of lesional areas among the 500 μm-spanning sections was referred as the aortic lesion score (μm^2/section). Cellular composition was assessed by immunohistochemical staining of alternating sections to those stained with Oil Red O, in 3 sections per animal and averaged over four animals per group. Assessment was performed for macrophages (MOMA-2, Beckman Coulter) and smooth muscle cells (smooth muscle α-actin, Spring Bioscience). Planimetric analysis was performed at 10X using ImagePro Plus software. Relative content of macrophages and/or smooth muscle cells was determined by the percentage of the positively-stained area over the entire lesional area.

Blood chemistry

Retro-orbital bleeding was performed under isoflurane anesthesia in 6-hour fasting animals, 1 week prior to the onset (5 weeks of age) as well as at the termination of the exposure protocols (11 weeks of age). Plasma total and HDL cholesterol were determined by enzymatic assays as previously described [3].

Monocyte Chemotaxis Assay

This assay evaluates the protective capacity of HDL against LDL-induced monocyte chemotactic activity. Monocytes were isolated from blood obtained from a large pool of healthy donors at the UCLA Division of Cardiology, Atherosclerosis Research Unit. Human aortic endothelial cells

GL14 Continued

(HAEC) and human aortic smooth muscle cells (SMC) were isolated from trimmings of fresh surgical aortic specimens from normal donor hearts during transplantation. Endothelial and smooth muscle cells were grown, propagated and used for forming an artery wall model in culture. Cocultures of HAEC and SMC were treated for 18 hours with a standard source of human LDL (100 μg LDL protein/ml), in the absence or presence of a standard source of human or murine HDL (50 μg HDL protein/ml). The LDL and HDL were isolated from normal standard plasma by FPLC[4]. The cells were then washed and incubated in fresh culture medium for 8 hours, following which supernatants were collected to assess monocyte chemotactic activity after 40-fold dilution, which is expressed as the number of monocytes that have transmigrated per high power field, HPF [4]. LDL-induced monocyte chemotactic activity is mostly (70 +/- 4%) a result of the induction of MCP1 secretion, stimulated by oxidized phospholipids that form during the oxidation of LDL by the artery wall cells to generate minimally oxidized LDL [5]. HDL ability to block monocyte chemotaxis correlates with its antioxidant capacity that decreases the generation of minimally oxidized LDL, resulting in inhibition of MCP1 induction and decreased monocyte binding and migration [6-8].

Lipid Peroxidation Assay

Malondialdehyde (MDA) content was measured in liver homogenates with a colorimetric assay (OxisResearch, OR) according to the manufacturer's instructions [9]. A standard curve was used to calculate the concentration (nmol/g) of MDA for each sample. The final MDA level represents the average of 14-16 age-matched animals/group.

RNA extraction and real-time RT-PCR

Total RNA was extracted from liver tissue with the Trizol method (Invitrogen). Reverse transcription was performed using 1 μg of RNA with the iScript cDNA Synthesis kit (Bio-Rad, Hercules, CA). Quantitative real-time polymerase chain reaction (qPCR) was used to measure tissue mRNA expression for heme oxygenase-1 (HO-1), NF-E2-related factor-2 (Nrf2), catalase, superoxide dismutase 2 (SOD2), NAD(P)H-quinone oxidoreductase 1 (NQO1), glutathione S-transferase-Ya (GST-Ya), activating transcription factor (ATF4) and β-actin, utilizing specific PCR primers [10]. The reactions were performed in duplicate on an ABI Prism 7000 (Applied

GL14 Continued

Biosystems, Foster City, CA, USA) using iQ Sybr Green Supermix (Bio-Rad). Reactions were performed with 0.4 μM of primers and 1 μg of cDNA template as follows: 95°C for 3 min, 40 cycles of 95°C for 15 sec, 58 - 64°C for 30 sec and 72°C for 30 sec. A standard curve was created from serial dilutions of a pooled sample of cDNA. Gene expression was normalized to β-actin. PCR levels were displayed as arbitrary units.

GL14 Continued

REFERENCES

1. Mehrabian M, Allayee H, Wong J, Shi W, Wang XP, Shaposhnik Z, Funk CD, Lusis AJ. Identification of 5-lipoxygenase as a major gene contributing to atherosclerosis susceptibility in mice. *Circ Res.* 2002;91:120-126.
2. Qiao JH, Xie PZ, Fishbein MC, Kreuzer J, Drake TA, Demer LL, Lusis AJ. Pathology of atheromatous lesions in inbred and genetically engineered mice. Genetic determination of arterial calcification. *Arterioscler Thromb.* 1994;14:1480-1497.
3. Warnick GR. Enzymatic methods for quantification of lipoprotein lipids. *Methods Enzymol.* 1986;129:101-123.
4. Navab M, Imes SS, Hama SY, Hough GP, Ross LA, Bork RW, Valente AJ, Berliner JA, Drinkwater DC, Laks H, et al. Monocyte transmigration induced by modification of low density lipoprotein in cocultures of human aortic wall cells is due to induction of monocyte chemotactic protein 1 synthesis and is abolished by high density lipoprotein. *J Clin Invest.* 1991;88:2039-2046.
5. Watson AD, Berliner JA, Hama SY, La Du BN, Faull KF, Fogelman AM, Navab M. Protective effect of high density lipoprotein associated paraoxonase. Inhibition of the biological activity of minimally oxidized low density lipoprotein. *J Clin Invest.* 1995;96:2882-2891.
6. Navab M, Hama SY, Anantharamaiah GM, Hassan K, Hough GP, Watson AD, Reddy ST, Sevanian A, Fonarow GC, Fogelman AM. Normal high density lipoprotein inhibits three steps in the formation of mildly oxidized low density lipoprotein: steps 2 and 3. *J Lipid Res.* 2000;41:1495-1508.
7. Navab M, Hama SY, Cooke CJ, Anantharamaiah GM, Chaddha M, Jin L, Subbanagounder G, Faull KF, Reddy ST, Miller NE, Fogelman AM. Normal high density lipoprotein inhibits three steps in the formation of mildly oxidized low density lipoprotein: step 1. *J Lipid Res.* 2000;41:1481-1494.
8. Navab M, Hama SY, Hough GP, Subbanagounder G, Reddy ST, Fogelman AM. A cell-free assay for detecting HDL that is dysfunctional in preventing the formation of or inactivating oxidized phospholipids. *J Lipid Res.* 2001;42:1308-1317.
9. Gerard-Monnier D, Erdelmeier I, Regnard K, Moze-Henry N, Yadan JC, Chaudiere J. Reactions of 1-methyl-2-phenylindole with malondialdehyde and 4-hydroxyalkenals. Analytical applications to a colorimetric assay of lipid peroxidation. *Chem Res Toxicol.* 1998;11:1176-1183.
10. Li N, Alam J, Venkatesan MI, Eiguren-Fernandez A, Schmitz D, Di Stefano E, Slaughter N, Killeen E, Wang X, Huang A, Wang M, Miguel AH, Cho A, Sioutas C, Nel AE. Nrf2 is a key transcription factor that regulates antioxidant defense in macrophages and epithelial cells: protecting against the proinflammatory and oxidizing effects of diesel exhaust chemicals. *J Immunol.* 2004;173:3467-3481.

GL14 Continued

Supplemental Table I. Cellular composition of atherosclerotic lesions

Group	MOMA-2 (%)	p (vs. FA)	SMC actin (%)	p (vs. FA)
FA	88±7	-	14±5	-
FP	86±2	0.60	10±5	0.58
UFP	88±3	0.91	5±7	0.42

MOMA-2 and SMC α-actin immunohistochemical staining were performed in 3 sections/animal (n=4 animals/group). Planimetric analysis was performed at 10X using ImagePro Plus software. Data shown represent mean ± SE of positive stained area/total lesion area x 100. Statistical analysis was performed by one-way ANOVA with Fisher's PLSD post hoc analysis. FA: filtered air, FP: fine particles, UFP: ultrafine particles.

GL14 Continued

Supplemental Table II. Plasma lipoproteins.

	Total cholesterol (mg/dl)	HDL cholesterol (mg/dl)
Baseline		
FA (n=17)	349 +/- 13	11 +/- 1
FP (n=17)	355 +/- 13	11 +/- 1
UFP (n=17)	352 +/- 12	11 +/- 1
End of protocol		
FA (n=16)	397 +/- 13	9 +/- 1
FP (n=16)	459/- 21†	8 +/- 1
UFP (n=15)	402 +/- 19	8 +/- 0.5

Mice were bled after 6-hour fasting. Baseline samples were collected one week prior to the beginning of exposure protocols. Samples taken at the end of the protocols were collected 24 hours after the last exposure. Values are given as mean ± SE (mg/dl). NM: not measured. † p (vs. FA group) ≤ 0.01, ‡ p (vs. UFP group) < 0.05. FA: filtered air, FP: fine particles, UFP: ultrafine particles.

GL14 Continued

Ultrafine Particulate Pollutants Induce Oxidative Stress and Mitochondrial Damage

Ning Li,[1,2] Constantinos Sioutas,[2,3] Arthur Cho,[2,4] Debra Schmitz,[2,4] Chandan Misra,[2,3] Joan Sempf,[5] Meiying Wang,[1,2] Terry Oberley,[5,6] John Froines,[2,3] and Andre Nel[1,2]

[1]Department of Medicine, University of California, Los Angeles, California, USA; [2]The Southern California Particle Center and Supersite, Los Angeles, California, USA; [3]Department of Civil and Environmental Engineering, University of Southern California, Los Angeles, California, USA; [4]Department of Molecular and Medical Pharmacology, University of California, Los Angeles, California, USA; [5]Pathology Service, Veterans Administration Medical Center, Madison, Wisconsin, USA; [6]Department of Pathology and Laboratory Medicine, University of Wisconsin, Madison, Wisconsin, USA; [7]Center for Occupational and Environmental Health, University of California, Los Angeles, California, USA

The objectives of this study were to determine whether differences in the size and composition of coarse (2.5–10 μm), fine (< 2.5 μm), and ultrafine (< 0.1 μm) particulate matter (PM) are related to their uptake in macrophages and epithelial cells and their ability to induce oxidative stress. The premise for this study is the increasing awareness that various PM components induce pulmonary inflammation through the generation of oxidative stress. Coarse, fine, and ultrafine particles (UFPs) were collected by ambient particle concentrators in the Los Angeles basin in California and used to study their chemical composition in parallel with assays for generation of reactive oxygen species (ROS) and ability to induce oxidative stress in macrophages and epithelial cells. UFPs were most potent toward inducing cellular heme oxygenase-1 (HO-1) expression and depleting intracellular glutathione. HO-1 expression, a sensitive marker for oxidative stress, is directly correlated with the high organic carbon and polycyclic aromatic hydrocarbon (PAH) content of UFPs. The dithiothreitol (DTT) assay, a quantitative measure of in vitro ROS formation, was correlated with PAH content and HO-1 expression. UFPs also had the highest ROS activity in the DTT assay. Because the small size of UFPs allows better tissue penetration, we used electron microscopy to study subcellular localization. UFPs and, to a lesser extent, fine particles, localize in mitochondria, where they induce major structural damage. This may contribute to oxidative stress. Our studies demonstrate that the increased biological potency of UFPs is related to the content of redox cycling organic chemicals and their ability to damage mitochondria. *Key words:* concentrated ambient particles, dithiothreitol assay, heme oxygenase-1, mitochondrial damage, oxidative stress, polycyclic aromatic hydrocarbon, ultrafine particles. *Environ Health Perspect* 111:455–460 (2003). doi:10.1289/ehp.6000 available via *http://dx.doi.org/* [Online 16 December 2002]

Epidemiologic studies have shown associations between ambient air particulate matter (PM) and adverse health outcomes, including increased mortality, emergency room visits, and time lost from work and school [Dockery et al. 1993; Health Effects Institute (HEI) 2002; Samet et al. 2000; Wichmann et al. 2000]. The underlying toxicologic mechanisms by which air pollutant particles induce adverse health effects are of intense scientific interest and have been earmarked as a key scientific priority by the National Academy of Sciences [National Research Council (NRC) 1998]. This includes a call for research on the physicochemical properties that promote particle toxicity (NRC 1998). PM with aerodynamic diameter < 2.5 μm ($PM_{2.5}$) is currently regulated by the U.S. Environmental Protection Agency. Within that spectrum of particle sizes, ultrafine particles (UFPs), defined as having an aerodynamic diameter < 0.1 μm, may have a central role in health effects of PM (Oberdörster and Utell 2002; Samet et al. 2000). Primary UFPs are formed during gas-to-particle conversion or during incomplete fuel combustion (HEI 2002). Due to their small size, high number concentration, and relatively large surface area per unit mass, UFPs have unique characteristics, including increased adsorption of organic molecules and enhanced ability to penetrate cellular targets in the lung and systemic circulation (Frampton 2001; HEI 2002; Nemmar et al. 2002; Oberdörster 1996; Utell and Frampton 2000).

Particle composition may also be critical in PM toxicity. We are interested in organic PM compounds because organic extracts made from diesel exhaust particles (DEPs) mimic intact particles in their ability to form reactive oxygen species (ROS) (Hiura et al. 1999, 2000; Kumagai et al. 1997; Nel et al. 1998). One of the major advances in PM research has been the recognition that the organic and metal PM components can induce proinflammatory effects in the lung due to their ability to cause oxidative stress (Kumagai et al. 1997; Nel et al. 1998, 2001; Saldiva et al. 2002). Quinones present in PM can act as catalysts to produce ROS directly and may be key compounds in PM-based oxidative stress (Monks et al. 1992; Penning et al. 1999). PAHs can induce oxidative stress indirectly, through biotransformation by cytochrome P450, epoxide hydrolase, and dihydrodiol dehydrogenase to generate redox active quinones [Penning et al. 1999). The involvement of quinones and PAHs was confirmed by demonstrating that compounds present in aromatic and polar fractions of DEP extracts mimic the pro-oxidative effects of intact particles in bronchial epithelial cells and macrophages (Li et al. 2000, 2002b). DEPs also induce cytochrome P450 1A1 induction in bronchial epithelial cells (Bonvallot et al. 2001). Animal and human experiments confirm that DEPs and PAHs derived from DEPs promote allergic airway inflammation and cytochrome P450 1A1 induction in the lungs of exposed mice (Miyabara et al. 1998; Nel et al. 1998; Takano et al. 2002; Tsien et al. 1997). Epidemiologic studies have also shown an association between PM exposure and asthma exacerbation (Nemmar et al. 2002; Penttinen et al. 2001; Utell and Frampton 2000).

The Versatile Aerosol Concentration Enrichment System (VACES), which uses three parallel sampling lines to collect concentrated ambient coarse, fine, and ultrafine particles for biological analysis, is now available for use in toxicologic studies aimed at identifying the relative toxicity of the different particle sizes (Kim et al. 2001a, 2001b). This technology enables us to probe the relationship between particle size, chemical composition, and toxicity (Li et al. 2002a). These concentrators are mobile and can be used to test hypotheses about particle toxicity in the Los Angeles basin in California. Concentrated air particulates (CAPs) of different sizes were collected to study their oxidative stress effects and subcellular localization in cultured macrophages and epithelial cells. We demonstrate that UFPs are more potent than fine (< 2.5 μm) or coarse (2.5–10 μm) particles

Address correspondence to A. Nel, Department of Medicine, UCLA School of Medicine, 52–175 CHS, 10833 Le Conte Avenue, Los Angeles, CA 90095 USA. Telephone: (310) 825-6620. E-mail: anel@mednet.ucla.edu

This study was supported by the National Institute of Environmental Health Sciences (grant RO1-ES10555) and the Southern California Particle Center and Supersite, funded by the U.S. Environmental Protection Agency (STAR award R827352-01) and the California Air Resources Board (grant 98–316).

This manuscript has not been subjected to the U.S. EPA peer and policy review.

Received 18 September 2002; accepted 16 December 2002.

GL14 Continued

toward inducing oxidative stress. This effect may be explained by adsorbed chemicals (organics and metals) capable of generating ROS and the ability of UFPs to localize in mitochondria.

Materials and Methods

Ambient particle collection. Ambient coarse particles (2.5–10 μm), fine plus ultrafine particles (< 2.5 μm), and UFPs (< 0.15 μm) were collected in the Los Angeles basin during November 2001–March 2002 using the VACES (Kim et al. 2001a, 2001b). Coarse particles were concentrated using a single nozzle virtual impactor, while fine and ultrafine particles were concentrated by drawing air samples through two parallel lines, using 2.5 μm and 0.15 μm cut-point preimpactors, respectively, to remove larger-sized particles. These particles are drawn through a saturation–condensation system that grows particles to 2–3 μm droplets, which are subsequently concentrated by virtual impaction. Highly concentrated particle suspensions were obtained by connecting the VACES output to a sterilized liquid impinger (BioSampler; SKC West Inc., Fullerton, CA) (Willeke et al. 1998). Aerosols were collected using ultrapure (Milli-Q; Millipore Corp., Bedford, MA) deionized water (resistivity 18.2 megaohm; total organic compounds < 10 ppb; particle-free; bacteria < 1 colony forming unit/mL) as the collection medium. The concentration enrichment process does not alter the physical, chemical, and morphologic properties of the particles (Kim et al. 2001a, 2001b). We determined the total amount of particulate loading in the collection medium by multiplying the ambient concentration of each PM mode by the total air sample volume collected by each VACES line. The particle concentration in the aqueous medium was then calculated by dividing the particle loading by the total volume collected in that time period. Five sample sets were collected, two at the University of Southern California (USC), and three at Claremont. USC is a typical urban site located 3 km south of downtown Los Angeles. This is a site in which aerosols are mostly generated from fresh vehicular emissions. Claremont is a receptor site approximately 45 km east (i.e., downwind) of downtown Los Angeles. In that location, ambient PM originates mostly from advection of polluted air parcels originally emitted in urban Los Angeles, after "aging" in the atmosphere for a few hours, as well as from secondary photochemical processes.

Particle chemical analysis. Samples were collected on Teflon and quartz filters with a Micro Orifice Uniform Deposit Impactor (MOUDI; MSP Corporation, Shoreview, MN) for chemical analysis (Li et al. 2002a). We used Teflon filters to determine the metal and trace element content by X-ray fluorescence and quartz filters to determine the organic carbon (MnO_2-catalyzed CO_2 formation), sulfate (ion chromatography), and nitrate (ion chromatography) contents (Li et al. 2002a). PAH content for each CAPs set was determined by an HPLC-fluorescence method that detects a signature group of 16 PAHs (Li et al. 2002a).

Cellular stimulation and heme oxygenase 1 (HO-1) immunoblotting. We used two cell lines in the study: RAW 264.7 and BEAS-2B. RAW 264.7 is a murine macrophage cell line that mimics the oxidative stress response of pulmonary alveolar macrophages in response to DEP exposure (Hiura et al. 1999, 2000; Li et al. 2002b). BEAS-2B is a transformed human bronchial epithelial cell line, which mimics the oxidative stress response of primary bronchial epithelial cells (Li et al. 2002b). For RAW 264.7 culture, particle suspensions were reconstituted with Dulbecco's Modified Eagle's Medium powder, a culture medium component that rapidly dissolves in deionized water. This culture medium was further replenished with 10% fetal calf serum and a 1:200 dilution of penicillin/streptomycin/amphotericin B (Li et al. 2002a). For BEAS-2B cells, particle suspensions were made up in hormonally defined F12 medium (Kawanski et al. 2001). After incubating cells for 16 hr, we used 100 μg of lysate protein for HO-1 immunoblotting (Li et al. 2000, 2002a, 2002b). Densitometric analysis was performed on a laser Personal Densitometer SI using ImageQuant software (both from Amersham Biosciences, Piscataway, NJ).

GSH/GSSG assay. Total glutathione and oxidized glutathione (GSSG) were measured in a glutathione reductase recycling assay (Tietze 1969). We calculated the amount of total glutathione and GSSG in the samples from the standard curves. The amount of reduced glutathione (GSH) was calculated by subtracting the amount of GSSG from that of the total glutathione.

DTT assay. The dithiothreitol (DTT) assay quantitatively measures the formation of ROS by quinone catalysis (Kumagai et al. 2002). In the presence of quinones, 1 mol DTT + 2 mol O_2 generate 1 mol DTT-disulfide + $2O_2^{\cdot-}$

a: Q + DTT → semi-Q + DTT-dihyl

b: Q + DTT-dihyl → semi-Q + DTT-disulfide

c: 2 semi-Q + $2O_2$ → 2Q + $2O_2^{\cdot-}$

Table 1. Mass concentration and fractional composition of CAPs collected in the Los Angeles basin.

	Claremont (n = 3)			USC (n = 2)		
Chemical composition	Coarse	Fine	Ultrafine	Coarse	Fine	Ultrafine
Mass concentration (μg/m³)	12.3	17.3	1.9	21.1	20.9	3.9
Organic carbon (%)	18	40	65	26	52	71
Elemental carbon (%)	1	3	13	1	3	11
Nitrate (%)	27	31	4	35	23	3
Sulfate (%)	5	13	5	7	8	6
Metals/other elements (%)	51	13	9	37	14	9

Values represent the mean fractional composition (%) in which SEM varied < 10%.

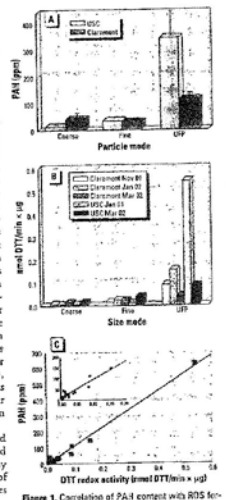


Figure 1. Correlation of PAH content with ROS formation. (*A*) PAH content for each set of CAPs determined by HPLC-fluorescence; values shown are mean ± SEM for Claremont (*n* = 3) and USC (*n* = 2). (*B*) In vitro electron transfer capacity of CAPs measured by a colorimetric assay that distinguishes oxidized from reduced DTT (Kumagai et al. 2002). The mean was calculated for three separate measurements; SEM < 0.1. (*C*) Linear regression analysis demonstrating the correlation between PAH content and 15 DTT data points (5 sites × 3 samples/site); r^2 = 0.96. Inset: With the highest point removed, r^2 remains significant at 0.86.

GL14 Continued

Net reaction: DTT + $2O_2$ → DTT-disulfide + $2O_2^{\cdot-}$

The loss of DTT is followed by its reaction with 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB), which is converted to 5-mercapto-2-nitrobenzoic (Kumagai et al. 2002). We incubated the PM sample (5–50 μg/mL) with 10 μM DTT in a Tris buffer at pH 8.9 for 10–90 min. Aliquots of the incubation mixture were transfered to the DNTB solution and the optical density read at 412 nm.

Electron microscopy. We performed electron microscopy as previously described (Yang et al. 1987). Thin sections were cut with a Reichert-Jung ultracut and ultramicrotome (Leica, Stuttgart, Germany). Copper grids were stained with lead citrate and uranyl acetate and photographed in a Hitachi electron microscope (Hitachi Instrument Inc., Tokyo, Japan).

Results

Particulate organic carbon and PAH content. To determine whether there is a link between UFP composition and biological effects, CAPs were collected at two outdoor sites in the Los Angeles basin with the VACES. Chemical analysis of the CAPs indicate that UFPs have a significantly higher organic ($p < 0.01$) and elemental carbon ($p < 0.001$) content than fine plus ultrafine (designated "fine") or coarse particles (Table 1). Coarse and fine particles had a higher metal content than UFPs (Table 1). PAH content for each set of CAPs was determined and averaged for both collection sites; there was a statistically significant difference in total PAH content in UFPs compared to fine ($p = 0.04$) and coarse ($p = 0.03$) PM (Figure 1A). The PAH content of UFPs at USC was significantly higher than the PAH content at Claremont (Figure 1A), which reflects the fact that particles collected at the source site (USC) are derived from primary emissions that are far more abundant in the urban areas of Los Angeles than in receptor areas.

The DTT assay of ROS formation by particles of varying size. The ability of PM to generate ROS was assessed with the DTT assay. Quinones with appropriate redox potentials can transfer electrons from DTT to oxygen (Kumagai et al. 2002). We used this reaction to determine the ability of PM to generate ROS *in vitro*. The DTT assay demonstrated that UFPs had significantly higher redox activity than fine and coarse PM (Figure 1B). Averaging of the data revealed that the redox cycling capacity of UFPs was 21.7- and 8.6-fold greater than coarse and fine PM, respectively (Figure 1B). Regression analysis of the DTT assay and PAH content showed a correlation coefficient (r^2) of 0.98, suggesting the electron transfer capacity of CAPs is consistent with their organic chemical content (Figure 1C).

Particle chemical composition and oxidative stress. Quinones and other redox-active compounds present in PM generate ROS and oxidative stress (Kumagai et al. 1997; Nel et al. 1998). We have demonstrated that DEP-induced oxidative stress generates hierarchical effects in pulmonary alveolar macrophages and bronchial epithelial cells (Li et al. 2002a, 2002b). Low levels of oxidative stress activate antioxidant defenses, whereas higher levels of oxidative stress lead to proinflammatory and cytotoxic effects (Li et al. 2002a, 2002b). An example of an antioxidant response is HO-1 expression via the antioxidant response element in its promoter (Choi and Alam 1996; Li et al. 2000). Utilizing an immunoblotting technique to assess HO-1 expression in RAW 264.7 cells, UFPs were more potent than fine or coarse particles (Figure 2A). Densitometric analysis demonstrated significantly higher HO-1 expression in ultrafine over fine ($p = 0.001$) and coarse ($p = 0.001$) particles, respectively.

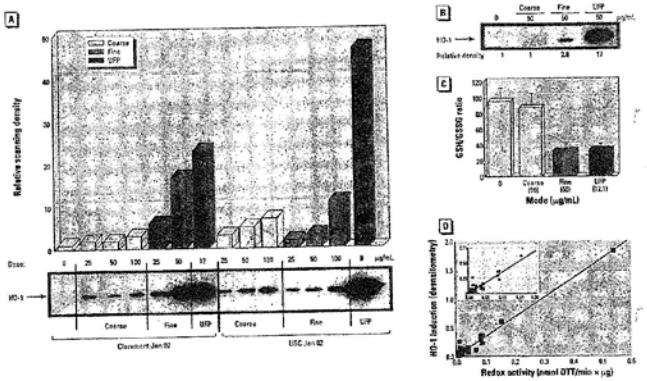


Figure 2. Induction of oxidative stress and HO-1 expression. (*A*) HO-1 expression in RAW 264.7 cells exposed to CAPs for 16 hr. (*B*) HO-1 expression in BEAS-2B cells treated with CAPs (Claremont Mar 02) for 16 hr. (*C*) Effects of CAPs (Claremont Jan 02) on the intracellular GSH/GSSG ratio in RAW 264.7 cells after 16 hr exposure; GSH/GSSG values shown are mean ± SEM from two separate experiments, with duplicate measurements per experiment (Tietze 1969). (*D*) Regression analysis demonstrating the correlation between *in vitro* redox activity of CAPs and HO-1 induction (15 data points); $r^2 = 0.67$. Inset: After removal of the highest data point, $r^2 = 0.81$.

GL14 Continued

The increased potency of UFPs was seen for all CAPs collections (data not shown).

Sufficient CAPs were collected in March 2002 to study HO-1 expression in the bronchial epithelial cell line, BEAS-2B, in parallel with RAW 264.7. The BEAS-2B response mimics the DEP-induced oxidative stress response in human bronchial epithelial cells (Li et al. 2002b). Immunoblot analysis shows that UFPs but not coarse or fine particles induce HO-1 expression in BEAS-2B cells (Figure 2B). To demonstrate that these effects reflect differences in the level of oxidative stress, we compared HO-1 expression to changes in the reduced (GSH) to oxidized (GSSG) glutathione ratio. These data show abundant HO-1 expression by UFPs or 50 μg/mL fine PM (Figure 2A, Claremont Jan 02), which is accompanied by a sizable drop in glutathione ratios (Figure 2C). In contrast, coarse particles had no effect on either biological response (Figure 2C). Regression analysis showed a correlation coefficient (r^2) of 0.97 between HO-1 expression and the DTT assay (Figure 2D). Overall, there is a strong correlation between particle size, chemical composition, ROS-generating capacity, and cellular oxidative stress.

UFP localization and mitochondrial damage. In defining the mechanistic features of PM toxicity, a key question is the subcellular localization of PM. This may determine ROS generation, as demonstrated by $O_2^{\cdot-}$ generation in lung microsomes during incubation with DEP extracts (Kumagai et al. 1997). Subcellular DEP targets include mitochondria, as demonstrated by the ability of organic DEP extracts to induce structural mitochondrial damage (Hiura et al. 1999, 2000; Li et al. 2002b). After exposure to CAPs, there were clear differences in the ultramicroscopic features of RAW 264.7 cells exposed to different particle sizes (Figure 3). Whereas coarse particles collected in large cytoplasmic vacuoles (Figure 3C and 3D), UFPs frequently lodged inside mitochondria (Figure 3G and H). Mitochondrial architecture remained intact in coarse PM incubations, but cells incubated with UFPs showed extensive disruption of mitochondrial cristae, resulting in a vacuolar cellular appearance (Figure 3H). These changes were time dependent, with fewer particles collecting inside mitochondria during shorter incubations (not shown). In cells exposed to fine particulates (which includes some UFPs), some particles lodged inside mitochondria but did not show the same degree of ultrastructural damage (Figure 3E and F).

Electron microscopy showed similar features in BEAS-2B cells—namely, considerable mitochondrial damage by UFPs, resulting in the formation of concentric structures, known as myelin figures (Figure 4). These structures result from the disassociation of lipoproteins, which facilitates water uptake and intercalation

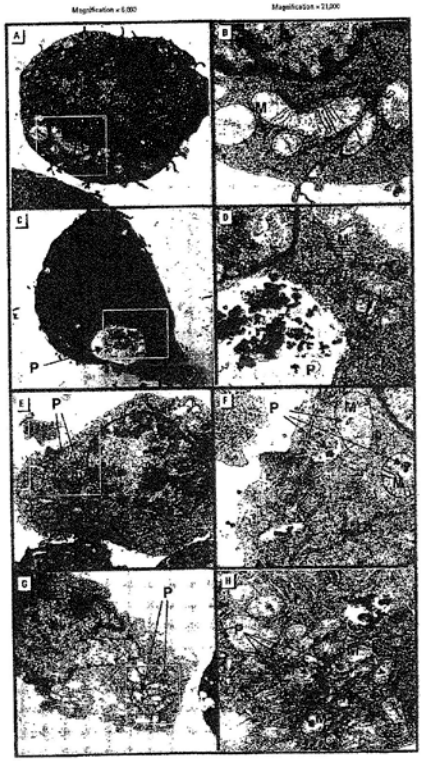


Figure 3. Electron micrographs demonstrating effects of different sized particles in RAW 264.7 cells treated with USC-Jan 02 CAPs for 18 hr. (*A*) and (*B*) Untreated RAW 264.7 cells. (*C*) and (*D*) RAW 264.7 cells exposed to coarse particles. (*E*) and (*F*) RAW 264.7 cells exposed to fine particles. (*G*) and (*H*) RAW 264.7 cells exposed to UFPs. Notice damage to cristae as well as the presence of particles (P) inside mitochondria (M) in UFP- or fine + UFP-exposed cells.

GL14 Continued

GL14 Continued

between lamellar membrane stacks (Figure 4C). Similar to RAW 264.7 cells, UFPs lodged inside damaged mitochondria (Figure 4C). Cells incubated with coarse or fine particles showed lesser mitochondrial damage (not shown). The extent of mitochondrial damage is in accordance with the redox cycling potential of the particles, as well as the HO-1 and glutathione results.

Discussion

Our data demonstrate that the UFP mode in the Los Angeles basin is more potent than fine and coarse PM toward inducing oxidative stress as measured by the DTT, HO-1, and glutathione assays. Electron microscopy also indicates subcellular penetration and mitochondrial damage by UFPs and, to a lesser extent, fine particles. The findings correlate with PM organic carbon and PAH composition, suggesting a role of organic agents in generating redox activity.

The results from the DTT assay indicate UFPs are capable of producing greater ROS on a microgram basis than fine and coarse particles. This is the first time that a quantitative assay has been used to directly measure ROS generation by CAPs. Kumagai et al. (2002) focused the assay on assessment of quinones, whereas we have applied the assay to UFPs and fine and coarse particles. The DTT assay provides a quantitative measure of the relative redox activity of different PM sizes in the Los Angeles basin.

UFPs contain a higher percentage of organic carbon than fine and coarse particles, and this has relevance to the biologic potency of these particles. The enhanced biologic potency of UFPs is directly correlated with the PAH content. Although PAHs are capable of inducing ROS production in macrophages, it is also possible that these compounds may be a surrogate for other redox cycling chemicals in the DTT assay. We do not exclude a contribution by transition metals, which may interact with organic PM components in ROS generation (Saldiva et al. 2002).

These data are in accordance with the growing awareness that oxidative stress plays a key role in the induction of airway inflammation (HEI 2002; Nel et al. 1998). Recently, we demonstrated that macrophages and epithelial cells exhibit a stratified oxidative stress response to increasing concentrations of DEPs (Li et al. 2002a, 2002b). The stratified response commences with HO-1 expression when the GSH/GSSG ratio is minimally disturbed, proceeds to *Jun* kinase activation at intermediary levels of oxidative stress, and culminates in cellular toxicity at high oxidative stress levels. Ambient CAPs mimic the effects of organic DEP extracts (Li et al. 2002a), with UFPs showing increased potency in depressing the cellular GSH/GSSG ratio (Figure 2C). The significance of *Jun* kinase activation is the transcriptional activation of cytokine, chemokine, and adhesion receptor promoters (Nel et al. 1998). These products play a role in the proinflammatory effects of PM in the lung and possibly also the cardiovascular system (Nel et al. 1998). The finding of a significant correlation between heme oxygenase activity, GSH/GSSG ratio, and redox activity as measured by DTT production provides further evidence for the role of ROS generation in PM toxicity.

The biological significance of HO-1 expression in the lung is the antioxidant effect of its catabolic product, bilirubin (Choi and Alam 1996). In the process of heme catabolism, HO-1 also generates a gaseous substance, CO, which exerts anti-inflammatory effects in the lung and is exhaled in the expired air (Horvath et al. 1998; Maines 1997). It is interesting, therefore, that in a study in which normal human volunteers were exposed to DEPs, CO levels in the expired air was a more sensitive exposure marker than the presence of inflammatory products in the bronchoalveolar fluid (Nightingale et al. 2000). This is in agreement with the exquisite sensitivity of the HO-1 promoter to oxidative stress *in vivo* and *in vitro* (Choi and Alam 1996; Nightingale et al. 2000). HO-1 expression and CO generation are markers for airway inflammation in asthma (Horvath et al. 1998). Monitoring of CO levels in the expired air may be a useful marker for evaluating the pro-oxidative and proinflammatory effects of CAPs in the respiratory tract.

How exactly UFPs gain access to and induce mitochondrial damage is unknown. One possibility is that ROS generated outside of the mitochondrion may damage this organelle, allowing access to the particles. This is compatible with the ability of organic DEP extracts to induce ultrastructural mitochondrial damage in the absence of particles (Hiura et al. 2000; Li et al. 2002b). Our previous studies have demonstrated that organic DEP chemicals induced pro-apoptotic effects in macrophages and bronchial epithelial cells (Hiura et al. 1999, 2000; Li et al. 2002b). This effect may be mediated through the perturbation of mitochondrial permeability transition pore, which sets in motion cytochrome *c* release, caspase activation, and superoxide production in the mitochondrial inner membrane (Hiura et al. 2000). Ultramicroscopic visualization of human macrophages and BEAS-2B cells incubated with organic DEP extracts showed that the appearance of apoptotic bodies were accompanied by changes in mitochondrial morphology, including mitochondrial swelling and a loss of cristae (Li et al. 2002b). Another possibility is that UFPs gain access to mitochondria because of their small sizes. These particles might then release redox cycling chemicals that damage the inner membrane. All considered, we propose that enhanced tissue penetrance and ability to generate oxidative stress render UFPs more damaging at cellular level and consequently contribute to the adverse health effects of UFPs in the Los Angeles basin.

These findings may be of importance for PM regulation. Currently, the manufacture of cleaner combustion engines relies on mass output standards but do not consider the output of large numbers of UFPs, which have very low mass. Our data show that UFPs are more potent than $PM_{2.5}$ and PM_{10} that contribute the majority of mass in the HO-1 and DTT assays. It may be necessary to consider standards based on particle number instead of mass if further studies confirm the differential toxicity of UFPs. Further research to more fully characterize the toxicity of UFPs in relation to particle number, surface area, and chemical composition is needed.

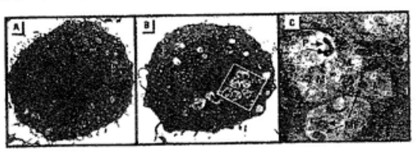


Figure 4. Electron micrographs demonstrating mitochondrial destruction in BEAS-2B cells treated with 8.4 µg/mL of USC-Jan 02 UFPs for 16 hr. (*A*) Untreated BEAS-2 cells; magnification ×8,500. (*B*) UFP-treated cells; magnification ×8,500. (*C*) UFP-treated cells; magnification ×26,300. Notice the disappearance of cristae, formation of myelin figures (MF), and presence of particles (P) inside mitochondria (M).

References

Bonvallot V, Baeza-Squiban A, Baulig A, Brulant S, Boland S, Muzeau F, et al. 2001. Organic compounds from diesel exhaust particles elicit a proinflammatory response in human airway epithelial cells and induce cytochrome P450 1A1 expression. Am J Respir Cell Mol Biol 25:515–521.

Choi AM, Alam J. 1996. Heme oxygenase-1: function, regulation, and implication of a novel stress-inducible protein in oxidant-induced lung injury. Am J Respir Cell Mol Biol 15:9–19.

Dockery DW, Pope CA, Xu X, Spengler JD, Ware JH, Fay ME, et

al. 1993. An association between air pollution and mortality in six U.S. cities. N Engl J Med 329:1753–1759.

Frampton MW. 2001. Systemic and cardiovascular effects of airway injury and inflammation: ultrafine particle exposure in humans. Environ Health Perspect 109(suppl 4):529–532.

HEI. 2002. Understanding the Health Effects of Components of the Particulate Matter Mix: Progress and Next Steps. Health Effects Institute Perspectives Series. Boston, MA:Health Effects Institute.

Hiura TS, Kaszubowski M, Li N, Nel AE. 1999. Chemicals in diesel exhaust particles generate reactive oxygen radicals and induce apoptosis in macrophages. J Immunol 163:5582–5591.

Hiura TS, Li N, Kaplan R, Horwitz M, Seagrave J, Nel AE. 2000. The role of a mitochondrial pathway in the induction of apoptosis by chemicals extracted from diesel exhaust particles. J Immunol 165:2703–2711.

Horvath I, Donnelly LE, Kiss A, Paredi P, Kharitonov SA, Barnes PJ. 1998. Raised levels of exhaled carbon monoxide are associated with an increased expression of heme oxygenase-1 in airway macrophages in asthma: a new marker of oxidative stress. Thorax 53:668–672.

Kawasaki S, Takizawa H, Takami K, Desaki M, Okazaki H, Kasama T, et al. 2001. Benzene-extracted components are important for the major activity of diesel exhaust particles. Am J Respir Cell Mol Biol 24:419–426.

Kim S, Jaques P, Chang MC, Froines JR, Sioutas C. 2001a. A versatile aerosol concentrator for simultaneous in vivo and in vitro evaluation of toxic effects of coarse, fine and ultrafine particles: Part I: Laboratory evaluation. J Aerosol Sci 11:1281–1297.

Kim S, Jaques P, Chang MC, Sioutas C. 2001b. Versatile aerosol concentration enrichment system (VACES) for simultaneous in-vivo and in-vitro evaluation of toxic effects of ultrafine, fine and coarse ambient particles. Part II: Field evaluation. J Aerosol Sci 11:1299–1314.

Kumagai Y, Arimoto T, Shinyashiki M, Shimojo N, Nakai Y, Yoshikawa T, et al. 1997. Generation of reactive oxygen species during interaction of diesel exhaust particle components with NADPH-cytochrome P450 reductase and involvement of the bioactivation in the DNA damage. Free Radic Biol Med 22:479–487.

Kumagai Y, Koide S, Taguchi K, Endo A, Nakai Y, Yoshikawa T, et al. 2002. Oxidation of proximal protein sulfhydryls by phenanthraquinone, a component of diesel exhaust particles. Chem Res Toxicol 15:483–489.

Li N, Kim S, Wang M, Froines J, Sioutas C, Nel AE. 2002a. Use of a stratified oxidative stress model to study the biological effects of ambient concentrated and diesel exhaust particulate matter. Inhalation Toxicol 14:459–486.

Li N, Venkatesan MI, Miguel A, Kaplan R, Gujuluva C, Alam J, et al. 2000. Induction of heme oxygenase-1 expression in macrophages by diesel exhaust particle chemicals and quinones via the antioxidant-responsive element. J Immunol 165:3393–3401.

Li N, Wang M, Oberley TD, Sempf JM, Nel AE. 2002b. Comparison of the pro-oxidative and pro-inflammatory effects of organic DEP chemicals in bronchial epithelial cells and macrophages. J Immunol 169: 4531–4541.

Maines MD. 1997. The heme oxygenase system: a regulator of second messenger gases. Annu Rev Pharmacol Toxicol 37:517–554.

Miyabara Y, Ichinose T, Takano H, Lim HB, Sagai M. 1998. Effects of diesel exhaust on allergic airway inflammation in mice. J Allergy Clin Immunol 102:805–812.

Monks TJ, Hanzlik RP, Cohen GM, Ross D, Graham DG. 1992. Quinone chemistry and toxicity. Toxicol Appl Pharmacol 112:2–16.

National Research Council (NRC). 1998. Research Priorities for Airborne Particulate Matter: I–Immediate Priorities and a Long-Range Research Portfolio. Washington, DC:National Academy Press.

Nel AE, Diaz-Sanchez D, Li N. 2001. The role of particulate pollutants in pulmonary inflammation and asthma: evidence for the involvement of organic chemicals and oxidative stress. Curr Opinion Pulmonary Med 7:20–26.

Nel AE, Diaz-Sanchez D, Ng D, Hiura T, Saxon A. 1998. Enhancement of allergic inflammation by the interaction between diesel exhaust particles and the immune system. J Allergy Clin Immunol 102:539–554.

Nemmar A, Hoet PH, Vanquickenborne B, Dinsdale D, Thomeer M, Hoylaerts MF, et al. 2002. Passage of inhaled particles into the blood circulation in humans. Circulation 105:411–414.

Nightingale JA, Maggs R, Cullinan P, Donnelly LE, Rogers DF, Kinnersley R, et al. 2000. Airway inflammation after controlled exposure to diesel exhaust particulates. Am J Respir Crit Care Med 162:161–166.

Oberdörster G. 1996. Significance of particle parameters in the evaluation of exposure-dose-response relationships of inhaled particles. Inhal Toxicol 8(suppl):73–89.

Oberdörster G, Utell MJ. 2002. Ultrafine particles in the urban air: to the respiratory tract—and beyond [Editorial]. Environ Health Perspect 110:A440–A441.

Penning TM, Burczynski ME, Hung CF, McCoull KD, Palackal NT, Tsuruda LS. 1999. Dihydrodiol dehydrogenases and polycyclic aromatic hydrocarbon activation: generation of reactive and redox active o-quinones. Chem Res Toxicol 12:1–18.

Peters A, Timonen KL, Tiittanen P, Mirme A, Ruuskanen J, Pekkanen J. 2001. Number concentration and size of particles in urban air: effects on spirometric lung function in adult asthmatic subjects. Environ Health Perspect 109:319–323.

Saldiva PH, Clarke RW, Coull BA, Stearns RC, Lawrence J, Murthy GG, et al. 2002. Lung inflammation induced by concentrated ambient air particles is related to particle composition. Am J Respir Crit Care Med 165:1610–1617.

Samet JM, Dominici F, Curriero FC, Coursac I, Zeger SL. 2000. Fine particulate air pollution and mortality in 20 U.S. cities, 1987–1994. N Engl J Med 343:1742–1749.

Takano H, Yanagisawa R, Ichinose T, Sadakane K, Inoue K, Yoshida S, et al. 2002. Lung expression of cytochrome P450 1A1 as a possible biomarker of exposure to diesel exhaust particles. Arch Toxicol 76:146–151.

Tietze F. 1969. Enzymic method for quantitative determination of nanogram amounts of total and oxidized glutathione: applications to mammalian blood and other tissues. Anal Biochem 27:502–522.

Tsien A, Diaz-Sanchez D, Ma J, Saxon A. 1997. The organic component of diesel exhaust particles and phenanthrene, a major polyaromatic hydrocarbon constituent, enhances IgE production by IgE-secreting EBV-transformed human B cells in vitro. Toxicol Appl Pharmacol 142:256–263.

Utell MJ, Frampton MW. 2000. Acute health effects of ambient air pollution: the ultrafine particle hypothesis. J Aerosol Med 13:355–359.

Wichmann HE, Spix C, Tuch T, Wolke G, Peters A, Heinrich J, et al. 2000. Daily mortality and fine and ultrafine particles in Erfurt, Germany. Part I: role of particle number and particle mass. Res Rep Health Eff Inst 98:5–86.

Willeke K, Lin X, Grinshpun SA. 1998. Improved aerosol collection by combined impaction and centrifugal motion. Aerosol Sci Tech 28:439–456.

Yang AH, Gould-Kostka J, Oberley TD. 1987. In vitro growth and differentiation of human kidney tubular cells on a basement membrane substrate. In Vitro Cell Dev Biol 23:34–46.

GL14 Continued

GL14 Continued

Research

Association of Biomarkers of Systemic Inflammation with Organic Components and Source Tracers in Quasi-Ultrafine Particles

Ralph J. Delfino,[1] Norbert Staimer,[1] Thomas Tjoa,[1] Mohammad Arhami,[2,3] Andrea Polidori,[3] Daniel L. Gillen,[4] Michael T. Kleinman,[5] James J. Schauer,[6] and Constantinos Sioutas[2]

[1]Department of Epidemiology, School of Medicine, University of California–Irvine, Irvine, California, USA; [2]Department of Civil and Environmental Engineering, Viterbi School of Engineering, University of Southern California, Los Angeles, California, USA; [3]Department of Civil Engineering, Sharif University of Technology, Tehran, Iran; [4]Department of Statistics, School of Information and Computer Sciences, University of California–Irvine, Irvine, California, USA; [5]Occupational and Environmental Medicine Division, Department of Medicine, School of Medicine, University of California–Irvine, Irvine, California, USA; [6]Environmental Chemistry and Technology Program, University of Wisconsin–Madison, Madison, Wisconsin, USA

BACKGROUND: Evidence is needed regarding the air pollutant components and their sources responsible for associations between particle mass concentrations and human cardiovascular outcomes. We previously found associations between circulating biomarkers of inflammation and mass concentrations of quasi-ultrafine particles ≤ 0.25 μm in aerodynamic diameter ($PM_{0.25}$) in a panel cohort study of 60 elderly subjects with coronary artery disease living in the Los Angeles Basin.

OBJECTIVES: We reassessed biomarker associations with $PM_{0.25}$ using new particle composition data.

METHODS: Weekly biomarkers of inflammation were plasma interleukin-6 (IL-6) and soluble tumor necrosis factor-α receptor II (sTNF-RII) (*n* = 578). Exposures included indoor and outdoor community organic $PM_{0.25}$ constituents [polycyclic aromatic hydrocarbons (PAHs), hopanes, *n*-alkanes, organic acids, water-soluble organic carbon, and transition metals]. We analyzed the relation between biomarkers and exposures with mixed-effects models adjusted for potential confounders.

RESULTS: Indoor and outdoor PAHs (low-, medium-, and high-molecular-weight PAHs), followed by hopanes (vehicle emissions tracer), were positively associated with biomarkers, but other organic components and transition metals were not. sTNF-RII increased by 135 pg/mL (95% confidence interval (CI), 45–225 pg/mL), and IL-6 increased by 0.27 pg/mL (95% CI, 0.10–0.44 pg/mL) per interquartile range increase of 0.56 ng/m^3 outdoor total PAHs. Two-pollutant models of $PM_{0.25}$ with PAHs showed that nominal associations of IL-6 and sTNF-RII with $PM_{0.25}$ mass were completely confounded by PAHs. Vehicular emission sources estimated from chemical mass balance models were strongly correlated with PAHs (R = 0.71).

CONCLUSIONS: Traffic emission sources of organic chemicals represented by PAHs are associated with increased systemic inflammation and explain associations with quasi-ultrafine particle mass.

KEY WORDS: air toxics, biomarkers of effect, cytokines, epidemiology, longitudinal data analysis. *Environ Health Perspect* 118:756–762 (2010). doi:10.1289/ehp.0901407 [Online 2 February 2010]

Cardiovascular hospital admissions and mortality have been associated with ambient mass concentrations of fine particulate matter (PM) air pollution ≤ 2.5 μm in aerodynamic diameter ($PM_{2.5}$) (Pope and Dockery 2006). Questions remain regarding the underlying causal chemical components and sources responsible for these associations. A recent time-series study of 106 U.S. counties showed stronger associations of cardiovascular hospital admissions with countywide averages of $PM_{2.5}$ when these were higher fractions of elemental carbon (EC), nickel (Ni), and vanadium (V), suggesting that important sources included fossil fuel combustion, biomass burning, and oil combustion (Bell et al. 2009).

Unlike $PM_{2.5}$, ultrafine particles (UFPs; generally defined as < 0.1 μm in diameter) are not regulated by the U.S. Environmental Protection Agency (EPA), yet this is the size fraction that may have the highest toxic potential because it has magnitudes greater number concentrations and surface area than the larger particles that dominate $PM_{2.5}$ mass (Oberdörster et al. 2005). On that large surface area, UFPs carry and deliver redox-active organic chemicals, including polycyclic aromatic hydrocarbons (PAHs), to the respiratory tract in disproportionately higher concentrations than do larger particles (Nel 2005; Nemmar et al. 2007), possibly leading to a cascade of effects related to oxidative stress and inflammation in the lungs and at extrapulmonary sites (Delfino et al. 2005). These and other effects could underlie associations of morbidity and mortality with air pollutants.

Except for some studies with personal or microenvironmental air pollution data (Chan et al. 2004; Delfino et al. 2008, 2009; Felino et al. 2009; Vinzents et al. 2005), regional ambient air monitoring has been the primary data source used in epidemiologic research on the importance of UFP exposure to cardiovascular outcomes and circulating biomarkers in individual-level studies (de Hartog et al. 2003; Henneberger et al. 2005; Ibald-Mulli et al. 2004; Lanki et al. 2008; Pekkanen et al. 2002; Rückerl et al. 2006, 2007; Timonen et al. 2006). These studies of ambient air were all conducted in Europe, and UFPs were measured as particle number concentrations at central regional sites. Exposure error from the use of ambient data is likely, because air monitors may be far from subject locations and subjects may be exposed to pollutants from local sources, including traffic. UFPs have much higher spatial variability than does $PM_{2.5}$ (Sioutas et al. 2005), so exposure error is likely. In addition, UFP mass and particle number do not specifically indicate which particle components or sources are important, although generally in urban areas UFP compositions are dominated by organic chemicals and EC and originate from combustion sources.

We conducted a panel cohort study of elderly subjects with a history of coronary artery disease living in the Los Angeles Basin. This is considered a population that may have among the greatest susceptibility to the adverse effects of air pollution (van Klot et al. 2005). We made repeated measurements of blood biomarkers and air pollutant exposures. To assess the potential importance of UFPs to cardiovascular health, we measured quasi-ultrafine particle mass < 0.25 μm in diameter ($PM_{0.25}$). To address the issue of exposure error, we monitored $PM_{0.25}$ at the retirement communities of subjects. We previously reported positive associations of blood biomarkers of inflammation with $PM_{0.25}$ but not with larger accumulation-mode particles 0.25–2.5 μm in diameter ($PM_{0.25-2.5}$) (Delfino et al. 2009). However, particle mass alone does not provide sufficient information about composition or sources. We also previously found positive associations between the biomarkers and $PM_{2.5}$ EC (Delfino et al. 2009). Based on these findings, we hypothesized that traffic emission sources of organic chemicals in $PM_{0.25}$ would be positively associated with systemic inflammation. In the present analysis, we aimed to better delineate which underlying PM components may be responsible for the associations we observed for EC and $PM_{0.25}$ mass using new data on chemical species in the archived $PM_{0.25}$ filter samples.

Address correspondence to R.J. Delfino, Department of Epidemiology, School of Medicine, University of California–Irvine, 100 Theory, Suite 100, Irvine, CA 92617-7555 USA. Telephone: (949) 824-1767. Fax: (949) 824-1343. E-mail: rdelfino@uci.edu

Supplemental Material is available online (doi:10.1289/ehp.0901407 via http://dx.doi.org/).

We appreciate the effort of staff from the Wisconsin State Laboratory of Hygiene; the Department of Epidemiology and General Clinical Research Center, University of California–Irvine; the Department of Civil and Environmental Engineering, University of Southern California; the California Air Resources Board; and the South Coast Air Quality Management District.

This project was supported by the National Institute of Environmental Health Sciences (grant ES12243) and the National Center for Research Resources (grant M01 RR00827) of the National Institutes of Health, by the California Air Resources Board (contract 03-329), and by the U.S. Environmental Protection Agency's Science to Achieve Results program (grant RD83241301) to the University of California–Los Angeles.

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the funding agencies, and no official endorsement should be inferred.

The authors declare they have no actual or potential competing financial interests.

Received 31 August 2009; accepted 2 February 2010.

Materials and Methods

Population and design. This was a longitudinal study of repeated measures where each subject acted as his or her own control over time. This limits the impact of confounding by between-subject characteristics. We recruited subjects from four retirement communities. Subjects were eligible for participation if they had a confirmed coronary artery disease history and were ≥ 65 years of age, nonsmokers, and unexposed to environmental tobacco smoke. Of 105 volunteers, 21 were not eligible, 19 dropped out, 2 had too few blood draws or valid biomarker data (> 5 of 12 weeks), and 3 had insufficient biomarker data due to exclusions for frequent infections, leaving 60 subjects. We excluded biomarker measurements during weeks with acute infectious illnesses given their well-known impact on measured biomarkers. Table 1 lists subject characteristics.

Two retirement communities were studied in 2005–2006 and two in 2006–2007. Subjects were followed for a total of 12 weeks with weekly blood draws for circulating biomarkers of inflammation in plasma. Each subject contributed 5–12 weekly blood draws (n = 578 total samples).

Each community was studied in two 6-week seasonal phases, a warmer period characterized by higher photochemistry followed by a cooler period characterized by higher air stagnation and lower mixing heights. This seasonal approach was intended to increase the variability in pollutant characteristics, with higher secondary organic aerosols (SOAs) in the warmer phase and higher primary organic aerosols (POAs) in the cooler phase when traffic-related air pollutants increase at ground level. POAs are formed during or shortly after the combustion of fossil fuels. SOAs are largely photochemically produced from gas-to-particle conversion when volatile reactive organic gases from anthropogenic and biogenic sources, and anthropogenic semivolatile organic compounds (SVOCs), are oxidized to form low-volatility products that condense to produce SOAs. There are few data on the importance of variations in this multipollutant characteristic of PM to human health outcomes. In the present study, POAs are represented by PAHs and hopanes, whereas SOAs are represented by water-soluble organic carbon (WSOC) and organic acids. Most PAHs are considered to be components of POAs. Hopanes are found in the lubricant oils of diesel and gasoline vehicles and are thus tracers of primary vehicular aerosols in the Los Angeles Basin (Schauer et al. 1996, 2000). WSOC (Snyder et al. 2009) and organic acids (Robinson et al. 2006) are tracers of SOAs, although a fraction of WSOC comes from biomass burning (Docherty et al. 2008).

The research protocol was approved by the Institutional Review Board of the University of California–Irvine, and we obtained informed written consent from subjects.

Biomarkers. We focused on an informative set of biomarkers of inflammation from the previous analysis of peripheral blood biomarkers and $PM_{0.25}$ mass (Delfino et al. 2009). We drew blood samples in ethylenediaminetetraacetic acid tubes on Friday afternoons and processed them and froze the plasma on site within 30 min. Samples were stored at –80°C until assayed. Plasma biomarkers were thawed and assayed using 96-well immunoassay kits for the proinflammatory cytokine interleukin-6 (IL-6) and the cytokine receptor–soluble tumor necrosis factor-α (TNF-α) receptor II (sTNF-RII; Quantikine HS, R&D Systems, Minneapolis, MN). sTNF-RII has a longer half-life than TNF-α (Aderka 1996) and may thus better reflect sustained or lagged effects. Thawed erythrocyte lysates were assayed spectrophotometrically for activities of the antioxidant enzymes copper/zinc-superoxide dismutase (Cu,Zn-SOD) and glutathione peroxidase-1 (GPx-1) (Cayman Chemical, Ann Arbor, MI, USA). Cu,Zn-SOD and GPx-1 values were normalized to units per gram of hemoglobin. These and related biomarkers are predictive of cardiovascular disease risk (Flores-Mateo et al. 2009; Kritchevsky et al. 2005; Pai et al. 2004).

Exposures. The methods used to measure components and their relevance to sources of $PM_{0.25}$ are described in detail in the Supplemental Material [Chemical Measurement Methods (doi:10.1289/ehp.0901407)] and by Arhami et al. (2010). There we also discuss in detail differences by season and community and describe the relation between indoor and outdoor measurements.

Air sampling occurred in the immediate outdoor environment of each retirement community and at an indoor site located in the common areas of the main community buildings. The indoor data are thus representative to some degree of the same indoor environment of each subject. Our main interest here is in the effects of outdoor-source PM components.

More than 5 days before each blood draw, we collected indoor and outdoor size-segregated particle samples using Sioutas Personal Cascade Impactors (SKC Inc., Eighty Four, PA, USA) with Zefluor filters (3-μm pore size; Pall Life Sciences, Ann Arbor, MI, USA). We evaluated components only in the quasi-ultrafine fraction ($PM_{0.25}$). Mass concentrations were determined gravimetrically by weighing the impactor filters and substrates with a microbalance (uncertainty, ± 2 μg; Mettler-Toledo, Columbus, OH, USA) in a temperature-controlled and relative humidity–controlled room.

The five weekly $PM_{0.25}$ filters were composited for chemical analyses. These composites were cut into three sections (one half-section and two quarter-sections). We analyzed the composited half section for 92 different organic compounds using gas chromatography/mass spectrometry (GC/MS) (Stone et al. 2008). For the present analysis, compounds are grouped by their structure, which is the primary control of their chemical interactions. Selected representative organic components were grouped as PAHs, organic (*n*-alkanoic) acids, *n*-alkanes, and hopanes [see Supplemental Material, Table 1 (doi:10.1289/ehp.0901407)]. PAHs were further subdivided into low- (two- to three-ring), medium- (four-ring), and high- (five-ring or larger) molecular-weight PAHs (LMW, MMW, and HMW, respectively), which is loosely connected to volatility and solubility.

Table 1. Subjects and biomarker outcomes.

Variable	Value
Age (years)	80.7 ± 5.60
Sex	
Male	34 (56.7)
Female	26 (43.3)
Cardiovascular history	
Confirmation of coronary artery disease[a]	
Myocardial infarction	27 (45.0)
Coronary artery bypass graft or angioplasty	20 (33.3)
Positive angiogram or stress test	10 (16.7)
Clinical diagnosis[b]	3 (5.0)
Congestive heart failure	13 (21.7)
Hypertension (by history)	42 (70.0)
Hypercholesterolemia (by history)	43 (71.7)
Medications	
Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists	24 (40.0)
3-Hydroxy-3-methylglutaryl-coenzyme A reductase-inhibitors (statins)	31 (51.7)
IL-6 (pg/mL)	2.42 ± 1.85
sTNF-RII (pg/mL)	3,810 ± 1,489

sTNF-RII, soluble tumor necrosis factor-α receptor II. Values are mean ± SD or n (%).
[a]Each category is hierarchical and excludes being in the above diagnostic category. [b]Includes subjects with original symptoms relieved with nitrates plus echocardiogram and electrocardiographic evidence of past infarct.

GL14 Continued

GL14 Continued

The first composited quarter-section was digested with concentrated acid using microwave digestion followed by analysis to determine 52 trace elements using high-resolution inductively coupled plasma mass spectrometry (Finnigan Element 2; Thermo Fisher Scientific, Waltham, MA, USA) (Herner et al. 2006). We focused our analyses of exposure–response relationships on key transition metals that can generate reactive oxygen species by Fenton-type reactions: vanadium (V), chromium (Cr), iron (Fe), nickel (Ni), copper (Cu), manganese (Mn), lead (Pb), and zinc (Zn).

The second composited quarter was analyzed for WSOC using a General Electric Sievers Total Organic Carbon Analyzer (GE Analytical Instruments, Boulder, CO, USA).

The remaining composited half was analyzed for organic tracer compounds by GC/MS along with field blanks, laboratory blanks, spiked samples, and standard reference material (Urban Dust Standard Resource Material 1649a; National Institute of Standards and Technology, Gaithersburg, MD, USA). Spike recovery after correction for internal standard recoveries was in the range of 96–110% for PAHs, 99–104% for hopanes, and 68–136% for *n*-alkanes. Blank concentrations of MMW PAHs, HMW PAHs, and hopanes were below analytical detection limits (~ 10 pg/m^3 air). The method detection limits for remaining compounds were limited by field and laboratory blanks. Uncertainties for each measurement were estimated based on analytical uncertainties and uncertainties from the blank correction and were used to determine if each measurement was statistically different from zero. The precision of the spike and standard reference material analyses was used to estimate method precision (> 20% for all PAHs, hopanes, and *n*-alkanes).

Statistical analysis. We analyzed relations of repeated (within-subject) measures of biomarkers to air pollutant exposures with linear mixed effects models. Random effects were estimated at the subject level, nested within seasonal phase and community, to account for correlated within-individual repeated measures. To focus estimates of associations at the subject level, we adjusted for between-community and between-phase exposure effects as proposed by Janes et al. (2008) by using exposures that were mean-centered across community and phase [see Supplemental Material, Regression Model, Mean Centering Method (doi:10.1289/ehp.0901407)]. We decided *a priori* to adjust for 5-day average temperature. Magnitudes of association from the mixed models are expressed as pollutant interquartile ranges (IQRs; 25th–75th percentile) to allow strengths of association for different pollutants to be compared by limiting differences due to units of measurement or concentration range.

We evaluated the covariance structure using empirical variograms and found models were best fit as an autoregressive-1 correlation structure. We performed residual analyses to examine deviations from standard linear mixed model assumptions and the presence of influential observations. We found four influential high outliers for IL-6 > 10 pg/mL that were reset to 10 pg/mL (upper limit of its standard curve) to obtain more representative estimates of association. In a model for 5-day average $PM_{0.25}$, including the outliers resulted in an association of 0.41 pg/mL [95% confidence interval (CI), 0.00–0.82] per interquartile change in $PM_{0.25}$ of 7.37 pg/m^3, whereas resetting them to 10 pg/mL resulted in an association of 0.26 pg/mL (95% CI, −0.05 to 0.57). It is important that in the previous analysis of $PM_{0.25}$ mass (Delfino et al. 2009), the associations with 1-day and 3-day average $PM_{0.25}$ were stronger and had narrower 95% CIs than did the 5-day average for both IL-6 and sTNF-RII.

In exploratory analyses, we retested models for erythrocyte antioxidant enzymes (Cu,Zn-SOD and GPx-1) from our previous publication (Delfino et al. 2009). Random slopes and individual autoregressive models showed small, highly influential subject clusters (seven subjects) with positive associations between air pollutants and antioxidant enzymes, whereas most of the remaining 53 subjects showed inverse associations. Details of these clusters and their interpretation are presented elsewhere (Delfino et al. 2009). We present these data-driven results with the new air pollutant exposure data primarily in the Supplemental Material, Table 3 (doi:10.1289/ehp.0901407).

Table 3. Exposure correlation matrix for outdoor $PM_{0.25}$ mass and organic components.

		PAH						
Pollutant	WSOC	Total	LMW	MMW	HMW	Hopanes	*n*-Alkanes	Organic acids
$PM_{0.25}$ mass	0.25	0.45	0.44	0.38	0.39	0.31	0.17	−0.16
WSOC	1.00	0.39	0.41	0.29	0.40	0.31	0.15	0.09
PAHs								
Total		1.00	0.89	0.83	0.81	0.54	0.15	−0.19
LMW			1.00	0.79	0.65	0.63	0.24	−0.24
MMW				1.00	0.87	0.51	0.12	−0.33
HMW					1.00	0.41	0.20	−0.03
Hopanes						1.00	0.08	−0.28
n-Alkanes							1.00	−0.06

All exposures are mean centered by study community and seasonal phase, and results are Spearman rank correlations.

Table 4. Exposure correlation matrix for outdoor PAH and source apportioned mass.

PAH	Vehicular emissions	Biomass burning	Ship emissions	SOAs	RS dust	NSS sulfate	Sea salt	Unknown
Total	0.71	0.22	0.19	0.19	0.24	0.05	0.33	0.33
LMW	0.79	0.14	0.17	0.27	0.39	0.10	0.34	0.51
MMW	0.68	0.26	−0.01	0.04	0.19	−0.06	0.27	0.30
HMW	0.65	0.28	0.09	0.27	0.13	0.13	0.15	0.14

Abbreviations: RS, resuspended; NSS, non-sea salt. All exposures are mean centered by study community and seasonal phase, and results are Spearman rank correlations. Source apportioned mass data come from Ashbaugh et al. (2010).

Table 2. Descriptive statistics of outdoor measurements and indoor/outdoor (I/O) ratios of $PM_{0.25}$ organic components and transition metals from 47 weeks of 5-day filter composites.

	Warm season				Cool season				
Exposure	Mean ± SD	IQR	Min/max	I/O ratio	Mean ± SD	IQR	Min/max	I/O ratio	IQR overall*
Organic components									
$PM_{0.25}$ mass (μg/m^3)	9.51 ± 3.46	7.24	4.67/14.7	0.86	8.65 ± 4.51	6.07	3.31/19.3	0.94	7.37
WSOC (μg/m^3)[a]	0.57 ± 0.23	0.31	0.08/1.01	0.85	0.38 ± 0.23	0.39	0.05/0.84	0.54	0.37
PAHs (ng/m^3)									
Total	0.68 ± 0.37	0.47	0.40/1.75	0.84	1.64 ± 0.81	0.73	0.43/2.70	0.59	0.56
LMW	0.39 ± 0.15	0.20	0.19/0.74	0.78	0.33 ± 0.15	0.19	0.17/0.73	1.02	0.19
MMW	0.26 ± 0.12	0.18	0.09/0.53	0.85	0.35 ± 0.24	0.33	0.08/0.96	0.74	0.24
HMW	0.24 ± 0.11	0.18	0.11/0.53	0.97	0.37 ± 0.24	0.32	0.14/1.01	1.04	0.21
Hopanes (ng/m^3)	0.27 ± 0.34	0.35	0.06/1.57	1.60	0.25 ± 0.25	0.35	0.06/0.93	0.97	0.35
n-Alkanes (ng/m^3)	36.3 ± 23.5	43.2	9.6/81.2	1.39	54.0 ± 111	15.9	11.2/500	1.30	20.4
Organic acids (μg/m^3)	0.27 ± 0.17	0.30	0.06/0.54	5.05	0.29 ± 0.22	0.28	0.07/0.96	1.24	0.29
Transition metals (ng/m^3)									
V	4.83 ± 2.07	2.10	1.66/11.3	0.75	2.19 ± 1.19	2.40	0.54/4.25	0.77	2.55
Cr	10.2 ± 39.2	2.21	0.00/139	0.69	0.26 ± 0.45	0.49	0.00/1.24	1.00	1.18
Mn	3.09 ± 2.88	2.10	0.00/13.8	0.57	2.02 ± 1.43	1.76	0.22/6.19	0.70	2.34
Fe	144 ± 127	167	0.00/568	0.49	92.5 ± 64.2	74.7	5.29/287	0.24	115
Ni	7.21 ± 18.0	2.51	0.00/62.8	0.83	0.20 ± 0.61	0.816	0.00/1.44	2.27	1.64
Cu	5.45 ± 4.35	5.50	0.35/16.0	0.64	4.68 ± 3.22	4.91	0.43/11.3	0.60	4.88
Zn	8.88 ± 4.16	6.39	0.00/15.8	0.78	5.08 ± 3.51	4.81	1.75/13.0	0.93	5.77

Abbreviations: max, maximum; Min, minimum.
*Overall IQR used in regression models to estimate expected change in the biomarker from exposure to the air pollutant. [a]WSOC (μg C/m^3) was multiplied by 1.8 to yield mass of organic components (μg/m^3) according to Turpin and Lim (2001).

Table 5. Associations of biomarkers of systemic effect with indoor and outdoor 5-day average $PM_{0.25}$ mass and organic components [regression coefficient (95% CI)].

Air pollutant	IL-6 (pg/mL)	sTNF-RII (pg/mL)
$PM_{0.25}$ mass		
Indoor	0.05 (−0.12 to 0.22)	18 (−61 to 97)
Outdoor	0.26 (−0.06 to 0.57)	125 (−40 to 289)
WSOC		
Indoor	−0.11 (−0.20 to 0.03)	15 (−77 to 168)
Outdoor	−0.09 (−0.27 to 0.10)	63 (−19 to 145)
PAHs		
Total		
Indoor	0.25 (0.07 to 0.43)**	119 (16 to 222)*
Outdoor	0.27 (0.10 to 0.44)**	135 (45 to 225)**
LMW		
Indoor	0.30 (0.10 to 0.52)**	115 (−2 to 233)
Outdoor	0.22 (0.05 to 0.39)*	109 (19 to 200)*
MMW		
Indoor	0.28 (0.07 to 0.48)**	138 (22 to 254)*
Outdoor	0.30 (0.12 to 0.49)***	143 (47 to 238)**
HMW		
Indoor	0.18 (0.02 to 0.35)*	91 (1 to 181)*
Outdoor	0.26 (0.07 to 0.44)**	137 (39 to 234)**
Hopanes		
Indoor	0.22 (0.04 to 0.38)*	107 (10 to 204)*
Outdoor	0.06 (−0.08 to 0.20)	85 (26 to 1517)**
n-Alkanes		
Indoor	0.01 (−0.03 to 0.05)	−6 (−27 to 16)
Outdoor	0.005 (−0.03 to 0.05)	14 (−6 to 34)
Organic acids		
Indoor	−0.05 (−0.22 to 0.12)	−36 (−109 to 37)
Outdoor	−0.22 (−0.38 to −0.05)**	−62 (−164 to 1)

Regression coefficients and 95% CIs are for the expected change in the biomarker among 69 subjects associated with an IQR change in the air pollutant [see Table 2], adjusted for temperature.
*$p < 0.05$, **$p < 0.01$.

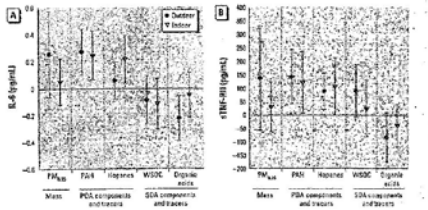


Figure 1. Associations of biomarkers with 5-day average outdoor and indoor community $PM_{0.25}$ mass, and markers of POAs and SOAs. (A) IL-6. (B) sTNF-RII. Expected change in the biomarker [adjusted coefficient and 95% CI] corresponds to an IQR increase in the air pollutant concentration (see Table 2), adjusted for temperature.

Results

Table 2 provides descriptive statistics for the measured exposures. Seasonal differences were greatest for MMW PAHs, HMW PAHs, and *n*-alkanes, which were higher in the cool season, and for WSOC, which was higher in the warm season, as expected because of photochemistry. Indoor/outdoor ratios were close to 1.0 for PAHs and hopanes, and indoor–outdoor correlations were strong (median R was 0.60 for PAH species and 0.74 for hopane species) (Arhami et al. 2010). This suggests high penetration of these outdoor $PM_{0.25}$ components into indoor environments and that measured indoor components were largely of outdoor origin. On the other hand, indoor/outdoor ratios were high for *n*-alkanes and *n*-alkanoic acids, with generally low indoor/outdoor correlation coefficients (Arhami et al. 2010). This suggests that indoor sources influenced the indoor levels of *n*-alkanes and *n*-alkanoic acids.

Table 3 shows a correlation matrix for measured outdoor organic components. We found moderate to strong correlations between $PM_{0.25}$ mass, PAHs, and hopanes. We also found small negative correlations of these species with organic acids and small positive correlations with WSOC, suggesting that POA and SOA concentrations are relatively independent of each other at the study sites.

To further improve our understanding of the clearly positive associations of biomarkers with summed PAH compounds presented below, we used the chemical mass balance model (CMB) source apportionment estimates from Arhami et al. (2010) to evaluate the possible sources of PAHs. We briefly summarize methods and source apportionment results in the Supplemental Material, Chemical mass balance (CMB) model (doi:10.1289/ehp.0901407). Table 4 shows a correlation matrix for the relation of PAHs to the CMB-estimated sources. Strong correlations are seen for total PAHs with vehicular emission sources, whereas the apportioned mass from other sources shows weak to null correlations.

In the mixed-model regression analyses, we found positive associations of circulating biomarkers of inflammation (IL-6 and sTNF-RII) with organic components (Table 5, Figure 1). We found the strongest associations with biomarkers for both indoor and outdoor PAHs, including LMW, MMW, and HMW PAHs. The next strongest associations were for hopanes. Indoor but not outdoor hopanes were associated with IL-6, whereas both indoor and outdoor hopanes were associated with sTNF-RII.

Outdoor WSOC (a marker of SOAs) was positively associated with sTNF-RII, but confidence limits crossed 1.0 ($p < 0.14$), and we found no other associations with SOA markers. The outdoor organic acids (another marker of SOAs) showed a pattern opposite to that of the POA markers, with largely negative regression coefficients in relation to biomarkers of inflammation. To assess whether this was due to inverse correlations with PAHs, we coregressed outdoor total PAHs with outdoor organic acids. We found that associations with PAHs and with organic acids decreased in magnitude to small degrees when coregressed, suggesting that the negative regression coefficients for organic acids with

GL14 Continued

biomarkers of inflammation may be attributed to other unmeasured factors or chance.

We then tested two-pollutant regression models that included both outdoor $PM_{0.25}$ mass and total PAHs to assess whether PAHs explained the nominal association with mass. We found that IL-6 and sTNF-RII associations with mass were completely confounded by PAHs in that the regression coefficient for mass decreased to just below zero and the regression coefficient for PAHs was nearly unchanged (Figure 2A,B). We found a similar effect for hopanes, which confounded the nominal association of $PM_{0.25}$ mass with sTNF-RII (Figure 2C). The variance inflation factor was < 3.5 for exposures, thus showing little evidence of multicollinearity.

Transition metals were not associated with the biomarkers [see Supplemental Material, Table 2 (doi:10.1289/ehp.0901407)].

As previously shown (Delfino et al. 2009), the analysis of the relation of erythrocyte antioxidant enzymes (Cu,Zn-SOD and GPx-1) to air pollutants among all 60 subjects showed regression coefficients were largely negative, suggesting inverse associations, but most upper confidence limits crossed 1.0 (see Supplemental Material, Table 3 (doi:10.1289/ehp.0901407)]. The exploratory analysis showed that among seven subjects previously identified as a "positive responder group" (Delfino et al. 2009), we found largely positive associations of Cu,Zn-SOD and GPx-1 with air pollutants, and lower confidence limits were > 1.0 for outdoor $PM_{0.25}$ mass and several other exposures. In the 53 subjects previously identified as a "negative responder group," we found inverse associations of Cu,Zn-SOD and GPx-1 with indoor and outdoor total, LMW, MMW, and HMW PAHs and with hopanes (all markers of exposures linked to primary combustion). Indoor WSOC was inversely ($p < 0.07$) associated with Cu,Zn-SOD, but we found no other associations with SOA markers in the negative responder group. Confidence limits were wider for GPx-1 than for Cu,Zn-SOD.

Discussion

To our knowledge, this is the first report from a panel cohort study to show associations of circulating biomarkers of response in human subjects to specific PM organic compound classes. The measured chemicals serve as indicators and tracers for air pollutant sources and for classes of chemicals with the potential for redox activity in the body. Our prior work has focused on carbonaceous aerosols that provided some differentiation between POAs and SOAs by showing associations of biomarkers of inflammation with primary $PM_{2.5}$ organic carbon (OC) but not secondary $PM_{2.5}$ OC (a marker of SOAs) (Delfino et al. 2008, 2009). In the present analysis, we found the strongest biomarker associations with air pollutant variables for all molecular weight classes of PAHs and specific source markers of vehicular emissions (hopanes) measured in $PM_{0.25}$ with GC/MS. Furthermore, two-pollutant models of the relation between the biomarkers of systemic inflammation and both total PAHs and $PM_{0.25}$ mass showed that mass associations were completely explained by PAHs. Given the results of the chemical mass balance analysis [see Supplemental Material, Chemical mass balance (CMB) model (doi:10.1289/ehp.0901407) and Arhami et al. 2010], we infer that the confounding of nominal associations between biomarkers and $PM_{0.25}$ mass by PAHs was through a common set of sources. PAHs likely serve here as a surrogate for redox-active PM chemical components as evidenced in experimental models (Riegel and Díaz-Sánchez 2005). For example, PAHs from diesel exhaust particles and oxidized derivatives of PAHs such as quinones lead to the generation of reactive oxygen species and subsequent oxidant injury and inflammatory responses, including the expression of nuclear transcription factor-κB (NFκB) (Riedl and Díaz-Sánchez 2005). NFκB increases the transcription of cytokines and acute-phase proteins that are predictive of coronary artery disease risk (Pai et al. 2004). PAHs can induce oxidative stress responses after biotransformation to quinones by cytochrome P450 1A1 (Bonvallot et al. 2001), perhaps after delivery from the lungs to systemic targets.

In the Los Angeles Basin, most outdoor PAHs in $PM_{0.25}$ are expected to be from mobile sources (Schauer et al. 1996), and the CMB exposure correlations are consistent with this expectation. PAHs were also correlated with source markers of vehicular emissions (hopanes). Hopanes are the most unambiguous source marker of traffic emissions. However, the moderate but not strong correlation between hopanes and PAHs suggests that the measured PAHs include a different subset of mobile sources than that of hopanes. This may in part be due to the variability in PAHs relative to hopanes by combustion-related problems in the vehicle fleet (Lough et al. 2007).

Overall, the associations of biomarkers with PAHs and hopanes suggest that our previous findings of positive associations of biomarkers with $PM_{2.5}$, EC, and primary OC (Delfino et al. 2009) were due to PM of mobile-source origin. PAHs are found in greater concentrations in the quasi-UFP range compared with larger particles (Ntziachristos et al. 2007), and this has been hypothesized to explain enhanced prooxidative and proinflammatory effects of urban UFPs in the lungs and peripheral target organs of rodents (Araujo et al. 2008). The increased biological potency of UFPs may be related to the content of organic chemicals that have the capacity to reduce oxygen, such as quinones and nitro-PAHs, for which PAHs may act, in part, as a surrogate (Ntziachristos et al. 2007) or as a source after biotransformation. From the present results we infer that, although PAHs may have an effect by

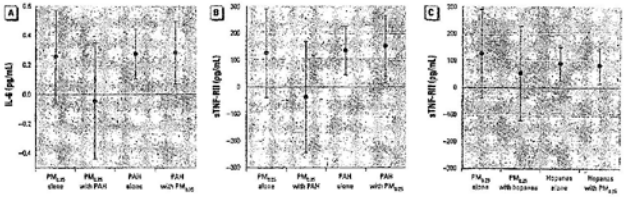


Figure 2. Associations of circulating biomarkers of inflammation with outdoor $PM_{0.25}$ mass corregressed with outdoor total PAHs and hopanes in $PM_{0.25}$. (*A*) IL-6, PAHs, and $PM_{0.25}$. (*B*) sTNF-RII, PAHs, and $PM_{0.25}$. (*C*) sTNF-RII, hopanes, and $PM_{0.25}$. Expected change in the biomarker (adjusted coefficient and 95% CI) corresponds to an IQR increase in the air pollutant concentration (see Table 2), adjusted for temperature.

GL14 Continued

themselves, they are also likely surrogates for other causal species we did not measure that are emitted from the same (traffic) sources.

We found little evidence that tracer variables for SOAs and related components (WSOC and organic acids) were associated with the circulating biomarkers in the expected direction. We have no explanation for the negative regression coefficients for organic acids with biomarkers. Although most of the SOAs are expected to be in larger PM > 0.25 μm, the present results are consistent with our finding of few biomarker associations with $PM_{2.5}$ secondary OC or accumulation mode particle mass ($PM_{0.25-2.5}$) in an earlier publication (Delfino et al. 2009). In that study, regression coefficients were also negative for IL-6 in some models with $PM_{0.25-2.5}$ and with secondary OC. We speculate that components in outdoor SOAs estimated by our methods (e.g., organic acids), are mostly water soluble and highly oxygenated, and dissolve after deposition on the airway epithelium and then quickly react with extracellular macromolecules and cell membrane constituents. Thus, these PM components may not directly interact with the vasculature, although it has been hypothesized that inhaled particles lead to airway inflammatory responses and subsequent release of activated leukocytes and cytokines into the circulation (Mills et al. 2009).

An important limitation of our characterization of SOAs is that WSOCs and organic acids do not completely characterize the SOA fraction of PM, part of which may come from the photochemical oxidation of low-volatility vapors to form hydrophilic organic components, but whose chemical identity is largely unknown. These precursor vapors include SVOCs that are largely part of POAs. SVOCs evaporate from the particle phase during the process of atmospheric dilution and subsequently react with oxidant gases to form a significant fraction of SOAs (Robinson et al. 2007).

Lipid-soluble components of PM more closely associated with primary emissions, including PAHs, may become bioavailable after deposition followed by distribution of unmetabolized chemicals to the circulation and to extrapulmonary target sites (Gerde et al. 2001). It is also possible that a small fraction of toxic components is carried via various translocation mechanisms into the circulation on UFPs (Mühlfeld et al. 2008). However, translocation may account for a potentially insignificant amount of the impact of UFPs compared with the high retention of UFPs in the lungs (Möller et al. 2008), which may lead to sustained effects through the gradual transfer of redox-active components to the circulation over many days.

Although transition metals are known to be redox active, we found no consistent associations with the biomarkers measured, possibly because of low concentrations of these trace elements in the study areas.

Finding positive associations of biomarkers with both indoor and outdoor PAHs and hopanes along with the indoor/outdoor ratios of these organic components being close to 1.0 suggests that, even though people spend most of their time indoors, indoor air quality and PM exposures are strongly influenced by PM of outdoor origin. These findings are consistent with our previous analysis for the first half of this panel showing that CMB–estimated indoor PM of outdoor origin (particle number, EC, and primary OC) were associated with the biomarkers to a similar degree as outdoor PM (Delfino et al. 2008).

Briefly, the exploratory (data-driven) findings for GPx-1 and especially Cu,Zn-SOD are consistent with our previous findings for primary OC and EC (Delfino et al. 2009) and suggest antioxidant enzyme inactivation within erythrocytes by traffic-related pollutant components, including PAHs, among a subgroup of people. This inactivation is anticipated to increase oxidative stress and thus inflammation. This is potentially important because these enzymes likely represent important intermediate end points that have been linked to the risk of developing coronary artery disease in prospective cohort and other studies (Flores-Mateo et al. 2009). Given that these findings were far less clear when including the entire 60-subject panel (because a small subgroup of seven subjects had positive associations), these results should be viewed as hypothesis generating and retested in other populations. See Delfino et al. (2009) for further details and discussion concerning potential mechanisms of antioxidant enzyme inactivation versus up-regulation that may explain group differences.

Strengths of the present study lie in exposure measurements in each subject's community microenvironment and in repeated biological marker assessments in a well-characterized patient sample. Limitations include the potential for unmeasured temporal confounding. However, we performed *a priori* adjustment for one of the largest sources of variability in inflammatory mediators that have been documented in the literature (infection), and we also accounted for temperature and for seasonality and seasonal variability in exposures. We also acknowledge that the present study does perform multiple comparisons, although we did narrow the number of hypotheses being tested based on prior evidence of associations from the work of others and ourselves.

The results of the present study suggest that tracer components of mobile source emissions in $PM_{0.25}$ are associated with increased systemic inflammation in a potentially susceptible population of elderly individuals. The measured biomarkers likely represent important intermediate end points (systemic inflammation) that have been linked to the risk of cardiovascular diseases in prospective cohort and other studies (Kritchevsky et al. 2005; Pai et al. 2004). The positive relation between air pollution and cytokine biomarkers may also be indicative of acute risk of adverse cardiovascular outcomes related to vascular dysfunction and athrothrombosis (Mills et al. 2009). We recently reported coherent associations between hourly ambulatory systolic and diastolic blood pressure and hourly air pollutant exposures in the present panel cohort, including stronger associations with primary $PM_{2.5}$ OC compared with secondary $PM_{2.5}$ OC (Delfino et al. 2010).

We conclude that U.S. EPA–regulated ambient $PM_{2.5}$ mass measurements may not adequately represent risk to human health because they are uncharacterized by composition, source, or PM size distribution and are not necessarily representative of personal or local exposure. Confirmatory data are needed in other populations using measurements of organic components across several PM size fractions.

References

Adams D. 1996. The potential biological and clinical significance of the soluble tumor necrosis factor receptors. Cytokine Growth Factor Rev 7:239–262.

Araujo JA, Barajas B, Kleinman M, Wang X, Bennett BJ, Gong KW, et al. 2008. Ambient particulate pollutants in the ultrafine range promote early atherosclerosis and systemic oxidative stress. Circ Res 102:589–596.

Arhami M, Minguillón MC, Polidori A, Schauer JJ, Delfino RJ, Sioutas C. 2010. Organic compound characterization and source apportionment of indoor and outdoor quasi-ultrafine PM in retirement homes of the Los Angeles Basin. Indoor Air 20(2):172–20.

Bell ML, Ebisu K, Peng RD, Samet JM, Dominici F. 2009. Hospital admissions and chemical composition of fine particle air pollution. Am J Respir Crit Care Med 179:1115–1120.

Bonvallot V, Baeza-Squiban A, Baulig A, Brulant S, Boland S, Muzeau F, et al. 2001. Organic compounds from diesel exhaust particles elicit a proinflammatory response in human airway epithelial cells and induce cytochrome P450 1A1 expression. Am J Respir Cell Mol Biol 25:515–521.

Chan C-C, Chuang KJ, Shiao GM, Lin LY. 2004. Personal exposure to submicrometer particles and heart rate variability in human subjects. Environ Health Perspect 112(10):1063–1067.

de Hartog JJ, Hoek G, Peters A, Timonen KL, Ibald-Mulli A, Brunekreef B, et al. 2003. Effects of fine and ultrafine particles on cardiorespiratory symptoms in elderly subjects with coronary heart disease: the ULTRA study. Am J Epidemiol 157:613–623.

Delfino RJ, Sioutas C, Malik S. 2005. Potential role of ultrafine particles in associations between airborne particle mass and cardiovascular health. Environ Health Perspect 113:934–946.

Delfino RJ, Staimer N, Tjoa T, Gillen D, Polidori A, Arhami M, et al. 2008. Air pollution exposures and circulating biomarkers of effect in a susceptible population: clues to potential causal component mixtures and mechanisms. Environ Health Perspect 116:1226–1235.

Delfino RJ, Staimer N, Tjoa T, Polidori A, Arhami M, Gillen D, et al. 2008. Circulating biomarkers of inflammation, antioxidant activity, and platelet activation are associated with urban air pollution in elderly subjects with a history of coronary artery disease. Environ Health Perspect 116:898–906.

Delfino RJ, Tjoa T, Gillen D, Staimer N, Polidori A, Arhami M, et al. 2010. Traffic-related air pollution and blood pressure in elderly subjects with coronary artery disease. Epidemiology 21:396–404.

GL14 Continued

Docherty KS, Stone EA, Ulbrich IM, DeCarlo PF, Snyder DC, Schauer JJ, et al. 2008. Apportionment of primary and secondary organic aerosols in Southern California during the 2005 Study of Organic Aerosols in Riverside (SOAR-1). Environ Sci Technol 42:7655–7662.

Flores-Mateo G, Carrillo-Santisteve P, Elosua R, Guallar E, Marrugat J, Bleys J, et al. 2009. Antioxidant enzyme activity and coronary heart disease: meta-analyses of observational studies. Am J Epidemiol 170:135–147.

Folino AF, Scapellato ML, Canova C, Maestrelli P, Bertorelli G, Simonato L, et al. 2009. Individual exposure to particulate matter and the short-term arrhythmic and autonomic profiles in patients with myocardial infarction. Eur Heart J 30:1614–1620.

Gerde P, Muggenburg BA, Lundborg M, Dahl AR. 2001. The rapid alveolar absorption of diesel soot-adsorbed benzo[a]pyrene: bioavailability, metabolism and dosimetry of an inhaled particle-borne carcinogen. Carcinogenesis 22:741–749.

Henneberger A, Zareba W, Ibald-Mulli A, Rückerl R, Cyrys J, Couderc JP, et al. 2005. Repolarization changes induced by air pollution in ischemic heart disease patients. Environ Health Perspect 113:440–446.

Herner JD, Green PG, Kleeman MJ. 2006. Measuring the trace elemental composition of size-resolved airborne particles. Environ Science Technol 40:1925–1933.

Ibald-Mulli A, Timonen KL, Peters A, Heinrich J, Wölke G, Lanki T, et al. 2004. Effects of particulate air pollution on blood pressure and heart rate in subjects with cardiovascular disease: a multicenter approach. Environ Health Perspect 112:369–377.

Janes H, Sheppard L, Shepherd K. 2008. Statistical analysis of air pollution panel studies: an illustration. Ann Epidemiol 18:792–802.

Kritchevsky SB, Cesari M, Pahor M. 2005. Inflammatory markers and cardiovascular health in older adults. Cardiovasc Res 66:265–275.

Lanki T, Hoek G, Timonen KL, Peters A, Tiittanen P, Vanninen E, et al. 2008. Hourly variation in fine particle exposure is associated with transiently increased risk of ST segment depression. Occup Environ Med 65:782–786.

Lough GC, Christensen CG, Schauer JJ, Tortorelli J, Mani E, Lawson DR, et al. 2007. Development of molecular marker source profiles for emissions from on-road gasoline and diesel vehicle fleets. J Air Waste Manage Assoc 57:1190–1199.

Mills NL, Donaldson K, Hadoke PW, Boon NA, MacNee W, Cassee FR, et al. 2009. Adverse cardiovascular effects of air pollution. Nat Clin Pract Cardiovasc Med 6:36–44.

Möller W, Felten K, Sommerer K, Scheuch G, Meyer G, Meyer P, et al. 2008. Deposition, retention, and translocation of ultrafine particles from the central airways and lung periphery. Am J Respir Crit Care Med 177:426–432.

Mühlfeld C, Gehr P, Rothen-Rutishauser B. 2008. Translocation and cellular entering mechanisms of nanoparticles in the respiratory tract. Swiss Med Wkly 138:387–391.

Ntziachristos L, Froines JR, Cho AK, Sioutas C. 2007. Relationship between redox activity and chemical speciation of size-fractionated particulate matter. Part Fibre Toxicol 4:5; doi: 10.1186/1743-8977-4-5 [Online 7 June 2007].

Oberdörster G, Oberdörster E, Oberdörster J. 2005. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ Health Perspect 113:823–839.

Pai JK, Pischon T, Ma J, Manson JE, Hankinson SE, Joshipura K, et al. 2004. Inflammatory markers and the risk of coronary heart disease in men and women. N Engl J Med 351:2599–2610.

Pekkanen J, Peters A, Hoek G, Tiittanen P, Brunekreef B, de Hartog J, et al. 2002. Particulate air pollution and risk of ST-segment depression during repeated submaximal exercise tests among subjects with coronary heart disease: the Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air (ULTRA) study. Circulation 106:933–938.

Pope CA III, Dockery DW. 2006. Health effects of fine particulate air pollution: lines that connect. J Air Waste Manag Assoc 56:709–742.

Riedl M, Diaz-Sanchez D. 2005. Biology of diesel exhaust effects on respiratory function. J Allergy Clin Immunol 115:221–228.

Robinson AL, Donahue NM, Rogge WF. 2006. Photochemical oxidation and changes in molecular composition of organic aerosol in the regional context. J Geophys Res-Atmos 111:D03302; doi:10.1029/2005JD006265 [Online 7 February 2006].

Robinson AL, Donahue NM, Shrivastava MK, Weitkamp EA, Sage AM, Grieshop AP, et al. 2007. Rethinking organic aerosols: semivolatile emissions and photochemical aging. Science 315:1259–1262.

Rückerl R, Ibald-Mulli A, Koenig W, Schneider A, Woelke G, Cyrys J, et al. 2006. Air pollution and markers of inflammation and coagulation in patients with coronary heart disease. Am J Respir Crit Care Med 173:432–441.

Rückerl R, Phipps RP, Schneider A, Frampton M, Cyrys J, Oberdörster G, et al. 2007. Ultrafine particles and platelet activation in patients with coronary heart disease—results from a prospective panel study. Part Fibre Toxicol 4:1; doi: 10.1186/1743-8977-4-1.

Schauer JJ, Cass GR. 2000. Source apportionment of wintertime gas-phase and particle-phase air pollutants using organic compounds as tracers. Environ Sci Technol 34:1821–1832.

Schauer JJ, Rogge WF, Hildemann LM, Mazurek MA, Cass GR. 1996. Source apportionment of airborne particulate matter using organic compounds as tracers. Atmos Environ 30:3837–3855.

Sioutas C, Delfino RJ, Singh M. 2005. Exposure assessment for atmospheric ultrafine particles (UFP) and implications in epidemiological research. Environ Health Perspect 113:947–955.

Snyder DC, Rutter AP, Collins R, Worley C, Schauer JJ. 2009. Insights into the origin of water soluble organic carbon in atmospheric fine particulate matter. Aerosol Sci Technol 43:1099–1107.

Stone EA, Snyder DC, Sheesley RJ, Sullivan AP, Weber RJ, Schauer JJ. 2008. Source apportionment of fine organic aerosol in Mexico City during the MILAGRO experiment 2006. Atmos Chem Phys 8:1249–1259.

Timonen KL, Vanninen E, de Hartog J, Ibald-Mulli A, Brunekreef B, Gold DR, et al. 2006. Effects of ultrafine and fine particulate and gaseous air pollution on cardiac autonomic control in subjects with coronary artery disease: the ULTRA study. J Expo Sci Environ Epidemiol 16:332–341.

Turpin BJ, Lim HJ. 2001. Species contributions to $PM_{2.5}$ mass concentrations: revisiting common assumptions for estimating organic mass. Aerosol Sci Technol 35:602–610.

Vinzents PS, Møller P, Sørensen M, Knudsen LE, Hertel O, Jensen FP, et al. 2005. Personal exposure to ultrafine particles and oxidative DNA damage. Environ Health Perspect 113:1485–1490.

von Klot S, Peters A, Aalto P, Bellander T, Berglind N, D'Ippoliti D, et al. 2005. Ambient air pollution is associated with increased risk of hospital cardiac readmissions of myocardial survivors in five European cities. Circulation 112:3073–3079.

GL14 Continued

Health Impacts of the Built Environment: Within-Urban Variability in Physical Inactivity, Air Pollution, and Ischemic Heart Disease Mortality

Steve Hankey,[1] Julian D. Marshall,[1] and Michael Brauer[2]

[1]Department of Civil Engineering, University of Minnesota, Minneapolis, Minnesota, USA; [2]School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada

BACKGROUND: Physical inactivity and exposure to air pollution are important risk factors for death and disease globally. The built environment may influence exposures to these risk factors in different ways and thus differentially affect the health of urban populations.

OBJECTIVE: We investigated the built environment's association with air pollution and physical inactivity, and estimated attributable health risks.

METHODS: We used a regional travel survey to estimate within-urban variability in physical inactivity and home-based air pollution exposure [particulate matter with aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$), nitrogen oxides (NO_x), and ozone (O_3)] for 30,007 individuals in southern California. We then estimated the resulting risk for ischemic heart disease (IHD) using literature-derived dose–response values. Using a cross-sectional approach, we compared estimated IHD mortality risks among neighborhoods based on "walkability" scores.

RESULTS: The proportion of physically active individuals was higher in high- versus low-walkability neighborhoods (24.9% vs. 12.5%); however, only a small proportion of the population was physically active, and between-neighborhood variability in estimated IHD mortality attributable to physical inactivity was modest (7 fewer IHD deaths/100,000/year in high- vs. low-walkability neighborhoods). Between-neighborhood differences in estimated IHD mortality from air pollution were comparable in magnitude (9 more IHD deaths/100,000/year for $PM_{2.5}$ and 3 fewer IHD deaths for O_3 in high- vs. low-walkability neighborhoods), suggesting that population health benefits from increased physical activity in high-walkability neighborhoods may be offset by adverse effects of air pollution exposure.

POLICY IMPLICATIONS: Currently, planning efforts mainly focus on increasing physical activity through neighborhood design. Our results suggest that differences in population health impacts among neighborhoods are similar in magnitude for air pollution and physical activity. Thus, physical activity and exposure to air pollution are critical aspects of planning for cleaner, health-promoting cities.

KEY WORDS: active travel, air quality, environmental planning, infill, risk assessment, urban form. *Environ Health Perspect* 120:247–253 (2012). http://dx.doi.org/10.1289/ehp.1103806 [Online 17 October 2011]

Physical inactivity is associated with increased risk of several adverse health outcomes including heart disease, type 2 diabetes, colon cancer, breast cancer, and mortality (Colditz et al. 1997; Kelley and Goodpaster 2001; Kohl 2001; Verloop et al. 2000). Active commuting, such as walking or biking to work on a daily basis, has been shown to decrease risk of all-cause mortality and cardiovascular disease (Andersen et al. 2000; Hamer and Chida 2008; Zheng et al. 2009). Various attributes of the built environment (e.g., population density, street connectivity, land use mix) have been associated with rates of physical activity at the neighborhood level (Ewing et al. 2003; Frank et al. 2005; Saelens et al. 2003a; Sallis et al. 2009). Furthermore, the type of transportation mode used (public transit vs. car) affects personal energy expenditure (Morabia et al. 2010). Thus, an important research question is whether urban planning can reduce physical inactivity and improve health.

Exposure to outdoor urban air pollution is associated with various adverse health outcomes including heart disease, respiratory disease, lung cancer, asthma, and mortality (Brunekreef and Holgate 2002; Gent et al. 2003; Pope and Dockery 2006; Pope et al. 2002). Chronic exposures vary at similar magnitudes within-cities as between-cities (Jerrett et al. 2005; Miller et al. 2007), suggesting that neighborhood location, urban design, and proximity to roads can affect exposures (Health Effects Institute 2009; Marshall et al. 2005).

Recently, the World Health Organization (WHO) cited physical inactivity (4th) and exposure to outdoor urban air pollution (14th) among the top 15 risk factors for the Global Burden of Disease (WHO 2009); for high-income countries, these ranks are 4th (physical inactivity) and 8th (outdoor air pollution). Urban planning and the built environment may differentially influence exposures to those two risk factors (Marshall et al. 2009). A small number of studies have investigated the effects of exercise while controlling for air pollution exposure (de Nazelle et al. 2009; Wong et al. 2007) or explored regional- or national-scale theoretical shifts to active travel (de Hartog et al. 2010; Grabow et al. 2011); however, accounting for health outcomes from exposure to air pollution and physical inactivity among neighborhood types is a little-studied area.

We used risk assessment to explore urban-scale spatial patterns in exposures associated with the built environment. We investigated differences in urban form that have been associated with physical inactivity and air pollution [specifically, particulate matter with aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$), nitrogen oxides (NO_x), and ozone (O_3)] to assess relationships between urban form and public health.

Methods

Our approach combined four primary sources of information: a geocoded, self-report travel diary to indicate home location and physical activity levels for a specific cohort ($n = 30,007$); modeled and measured estimates of outdoor air pollution concentrations and their variability in space and time; literature-derived estimates relating ischemic heart disease (IHD) rates with physical inactivity and exposure to air pollution; and geographic information system (GIS) land use variables related to walkability. Our method is descriptive (i.e., cross-sectional) and aims to explore long-term health effects of neighborhood characteristics and location. Figure 1 illustrates our risk assessment approach.

Physical inactivity and air pollution exposures. We used the year 2001 Post-Census Regional Travel Survey to estimate exposure to physical inactivity and home-based exposure to outdoor air pollution. This survey, which covers southern California communities such as Orange County and Los Angeles, included a geocoded time–activity

Address correspondence to J. Marshall, 500 Pillsbury Dr. SE, University of Minnesota, Minneapolis, MN 55455 USA. Telephone: (612) 625-2397. Fax: (612) 626-7750. E-mail: julian@umn.edu

Supplemental Material is available online (http://dx.doi.org/10.1289/ehp.1103806).

Research was partially conducted while S.H. and J.D.M. were visiting researchers at the Centre de Recerca en Epidemiologia Ambiental (CREAL; Center for Research in Environmental Epidemiology), Barcelona, Spain. We thank several CREAL researchers, including A. de Nazelle, M. Nieuwenhuijsen, D. Rojas-Rueda, and others in the Transportation, Air Pollution, and Physical Activities project for helpful feedback. The three anonymous reviewers provided excellent comments.

The authors declare they have no actual or potential competing financial interests.

Received 11 April 2011; accepted 17 October 2011.

GL14 Continued

diary that captured self-reported activities and travel during fall 2001 and spring 2002. The survey population consisted of a random sample of residents, recruited by telephone in six southern California counties [Imperial, Los Angeles, Orange, Riverside, San Bernardino, and Ventura; for survey details, see Southern California Association of Governments (SCAG 2003)]. To our knowledge, no other metropolitan-scale travel survey has been used to estimate physical activity and exposure to air pollution (Marshall et al. 2006); in addition, this survey represents one of the largest exposure-relevant surveys available for any urban area in the world.

Of the 40,376 survey respondents, 30,007 (74%) met our inclusion criteria: *a*) geocoded home location [2,346 respondents excluded (5.8%)], *b*) home location within the air pollution modeling domain—the South Coast Air Basin [4,491 respondents excluded (11.1%)], and *c*) complete demographic information [age, sex, and ethnicity; 3,532 respondents excluded (8.7%)]. The survey generally covered 1 weekday per participant. We multiplied each participant's 1-day physical activity record by 7 to obtain an estimate of weekly minutes of physical activity. This approach assumed that physical activity was constant across all days of the week. Population-average levels of physical activity were similar (< 15% difference) between weekdays and weekends (11 vs. 12 min/day, respectively) based on data from a small number of respondents (13%, $n = 5,104$) who participated in an additional weekend survey supplement (see sensitivity analysis 1, below). The survey recorded total physical activity and separately disaggregated that total into active transport (e.g., walking, bicycling) versus recreational activities (e.g., sports, working out at a gym).

Our primary estimates for air pollution exposure were based on monitoring data [U.S. Environmental Protection Agency (EPA) 2010] for $PM_{2.5}$, NO_x, and O_3 in 2001. We interpolated concentrations [inverse-distance weighted average of the nearest three monitors (Marshall et al. 2008)] to each survey participant's home location. Each pollutant had several monitoring stations ($PM_{2.5}$, 27; NO_x, 42; O_3, 52), providing good spatial coverage for the 36,000-km² study area. We estimated the annual average of daily 1-hr maximum concentrations for O_3 and annual-average concentrations for $PM_{2.5}$ and NO_x at each survey participant's residence to match the metrics used in the epidemiological studies that we used to estimate IHD risks. We used spatial interpolation for the base case because it can be used for all three pollutants and is easily transferable to other urban areas.

Neighborhood walkability. We calculated three built environment variables to represent neighborhood type: *a*) population density, *b*) intersection density, and *c*) land use mix. Neighborhoods that were in the upper (lower) tertile of all three built environment variables were defined as high- (low-) walkability neighborhoods. This approach classified 12% of the survey population as living in a high-walkability neighborhood and 18% as living in a low-walkability neighborhood. We used objective measurements of the built environment rather than geographical overlays to match methods commonly used in the urban planning literature. Although no standard measure of walkability exists, most indices include measures of density, connectivity, and land use mix (Ewing and Cervero 2001). As a sensitivity analysis, based on prior research (Marshall et al. 2009) we implemented a second definition that classified 33% of survey participants in high- and 33% in low-walkability neighborhoods [for methods, see Supplemental Material, p. 2 (http://dx.doi.org/10.1289/ehp.1103805)]. Results were similar for both definitions; therefore, we report results using the first definition only.

Population density. We used U.S. Census data from the year 2000 to calculate population density at the tract level for each household (U.S. Census Bureau 2000). Population density has been shown to be a predictor of per capita automobile travel (Holtzclaw et al. 2002; Marshall 2008) and trip length (Ewing and Cervero 2001), both of which are predictors of bicycling and walking (Handy et al. 2002).

Intersection density. Intersection density was calculated using road TIGER/Line data (U.S. Census Bureau 2000). A 1-km non-freeway network buffer was generated for each household using ArcGIS (version: 9.3.1, ESRI; Redlands, CA, USA). Intersections (more than two road segments) were summed within the buffer, yielding a measure of street connectivity. Previous studies show that street connectivity may reduce vehicle travel and increase walking (Ewing and Cervero 2001; Forsyth et al. 2008).

Land use mix. Following Frank et al. (2004), we calculated a land use mix index for each household location. Aerial land use data was obtained from SCAG for the year 2001 (SCAG 2010). The index [see Supplemental Material, pp. 2–3 (http://dx.doi.org/10.1289/ehp.1103806)] is a normalized ratio of the mix of four primary land uses (residential, commercial, retail, and institutional) to total land area within the 1-km network buffer. The index ranges from 0 to 1: A value of 1 represents an equal mixture of the four land uses; a value of 0 indicates 100% of land is a single land use. Impacts of land use mix on health include reducing obesity (Frank et al. 2005) and increasing physical activity (Saelens et al. 2003b).

Dose–response and relative risk estimates. For each survey participant (i.e., at the individual level), we estimated relative risks (RRs) attributable to outdoor air pollution and physical inactivity for one important health outcome: IHD. IHD is consistently associated with outdoor air pollution and physical inactivity (WHO 2009), is responsible for a large proportion of deaths in the United States (~ 18% of all deaths and 67% of heart disease deaths in 2006) [Centers for Disease Control and Prevention (CDC) 2009], and has been shown to be an important health outcome for both risk factors when considering large-scale shifts to active travel (Woodcock et al. 2009). Because our exposure estimates for air pollution are continuous, we estimated an RR for each survey participant based on a linear dose–response [see Supplemental Material, Figure S2 (http://dx.doi.org/10.1289/ehp.1103806)] for the range of observed air pollutant concentrations and the referent exposure levels described below. In contrast, WHO (2004) suggests a three-tier dose–response for physical activity: *a*) active (exercise for > 150 min/week; RR = 1), *b*) insufficiently active (exercise for 1–150 min/week; RR = 1.31), and *c*) inactive (0 min exercise per week; RR = 1.47), allowing for only three possible physical activity RRs for each survey participant. We estimated

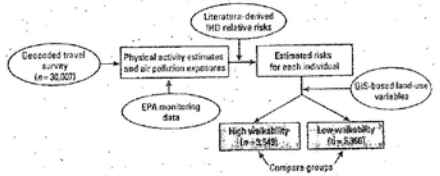


Figure 1. Conceptual framework for this risk assessment. Ovals are inputs, and boxes are midpoint calculations. Shaded boxes indicate estimated risk separated into two groups for comparison.

GL14 Continued

attributable fractions for outdoor air pollution and physical inactivity using the mean individual RR in high- or low-walkability neighborhoods.

Air pollution dose–response relationships were identified and selected as follows. We manually searched the tables of contents of four journals (*Journal of the American Medical Association*, *New England Journal of Medicine*, *British Medical Journal*, *Lancet*) for the years 2000–2010 for air pollution risk estimates. We also performed a search of key words in Google Scholar and ISI Knowledge, including (in various combinations) "air pollution," "O_3/NO_x/$PM_{2.5}$," "ischemic heart disease," "cardiovascular disease," "cardiopulmonary disease," "respiratory disease," "mortality," "health effects," "chronic/acute," and "dose–response." We used the "cited by" function in Google Scholar to explore subsequent studies related to each article. Through this process, we identified 62 articles. We then selected studies that focused on within-city variation and included IHD as a health outcome (Table 1).

Each RR for air pollution was estimated from cohort studies of long-term exposures; however, these estimates differed in important ways. For example, Nafstad et al. (2004) studied men 40–49 years of age, meaning our NO_x results cannot be generalized to other populations [RR = 1.08; 95% confidence interval (CI): 1.06, 1.11]. Jerrett et al. (2005) used a subset of the American Cancer Society (ACS) cohort (Los Angeles, CA, USA) to estimate a within-city RR of 1.25 per 10 μg/m³ increase in $PM_{2.5}$ (95% CI: 0.99, 1.59). Jerrett et al. (2005) did not report a significant RR for $PM_{2.5}$ in Los Angeles, but the RR estimate is roughly consistent with two between-city studies that did report statistically significant RRs: Pope et al. (2004; RR = 1.18 per 10 μg/m³ increase in $PM_{2.5}$; 95% CI: 1.14, 1.23) and Jerrett et al. (2009; RR = 1.21; 95% CI: 1.16, 1.27). The Jerrett et al. (2009) RR for a 10 μg/m³ increase in O_3 (1.008; 95% CI: 1.002, 1.013) was based on between-city variation (ACS cohort) in 96 U.S. metropolitan statistical areas generated from a one-pollutant model. However, it is important to note that Jerrett et al. (2009) reported a protective effect for O_3 based on a two-pollutant model adjusted for $PM_{2.5}$ (RR = 0.97; 95% CI: 0.96, 0.99), and overall there is less evidence in the literature for O_3 associations with IHD compared with those for $PM_{2.5}$. A within-city study of O_3 and IHD was not available.

The referent exposure levels used to estimate individuals' RRs were "active" for physical inactivity (> 150 min of moderate-vigorous activity per week), and the 10th percentile of exposure (survey population based; values: 13.6 μg/m³ for $PM_{2.5}$, 39.8 μg/m³ for NO_x, 80.3 μg/80.3 μg/m³ for O_3) for air pollution, consistent with exposures in a relatively clean neighborhood in the study area. Each survey participant's air pollution RR was estimated based on the difference between their home-location air pollution exposure and the referent exposure level. For example, for $PM_{2.5}$, an individual whose home-location exposure estimate was 25.6 μg/m³ (10 μg/m³ above the referent level) would be assigned an RR of 1.25.

Population-attributable fraction. We calculated population-attributable fraction (PAF) and estimated attributable IHD mortality rates for each risk factor in high- and low-walkability neighborhoods. PAF for a neighborhood was calculated based on the proportion of individuals exposed to each risk factor and average RR among all individuals in a neighborhood (Baker and Nieuwenhuijsen 2008):

$$\mathrm{PAF} = \frac{p \times (\mathrm{RR} - 1)}{[p \times (\mathrm{RR} - 1)] + 1}. \quad [1]$$

Here, RR is the mean individual RR in each group (high- and low-walkability neighborhood) and risk factor, and p is the proportion of individuals exposed in each group (defined by our referent exposure level). We used the 2000–2001 age-adjusted IHD mortality rate in California (191.2 IHD deaths/100,000/year; CDC 2011) to estimate deaths within each group and subsequent attributable IHD mortality rates (except for NO_x where we used the IHD mortality rate for men in California 45–54 years of age: 81.9 IHD deaths/100,000/year). Attributable mortality due to physical inactivity, $PM_{2.5}$, NO_x, and O_3 cannot be summed because of confounding among the risk factors and overlap of at-risk populations. Therefore, we report attributable mortality due to the different factors separately.

We separately calculated PAF using a method with multiple exposure levels instead of the dichotomous exposure levels implicit in Equation 1, as described in the Supplemental Material [pp. 5–6 (http://dx.doi.org/10.1289/ehp.1103806)] Results based on this alternative method were similar to those reported below.

Sensitivity analyses. To explore the robustness of our estimates, we used three sensitivity analyses to assess *a*) different methods of scaling minutes of physical activity, *b*) alternate modeling approaches for air pollution, and *c*) stepwise versus linear dose–response for physical activity.

Sensitivity analysis 1: scaling method for minutes of physical activity. Our approach requires extrapolating weekly exercise rates based on the 1-day travel diary because most physical activity epidemiological literature employs the metric "minutes of physical activity per week." To test the limitations of this extrapolation for our analysis, we developed a Monte Carlo simulation that relaxes our base-case assumption (i.e., that individuals' physical activity rates are constant by day), by employing two alternative assumptions: that people who are nonsedentary are physically active *a*) every other day or *b*) every third day. The Monte Carlo simulation distributes total minutes of physical activity accordingly, stratifying by age, sex, and ethnicity. The resulting distributions of physical activity better approximate national estimates on the prevalence of physical inactivity (WHO 2004).

Sensitivity analysis 2: air pollution model. Our base-case analysis used spatial interpolation of U.S. EPA monitoring data, which are readily available for all three pollutants for many urban areas. We compared results using a Eulerian dispersion model [Comprehensive Air Quality Model with Extensions (CAMx); http://www.camx.com; nitrous oxide (NO), nitrogen dioxide (NO_2), O_3] and land-use regression (LUR; NO_2; Novotny et al. 2011). CAMx and LUR provide greater spatial precision than inverse-distance weighting but may or may not be available in other urban areas.

Sensitivity analysis 3: physical activity dose–response. We tested the sensitivity of our results to the dose–response curve for physical inactivity. Our base case used the stepwise dose–response from WHO (2004) (Table 1). For this sensitivity analysis, we generated three linear dose–response curves (low, medium, and high slopes) based on the same WHO values.

Results

Annual-average air pollution exposure for the survey population averaged 49 μg/m³ for NO_2 [interquartile range (IQR), 41–60 μg/m³), 99 μg/m³ for O_3

Table 1. Summary of RR estimates used for IHD.

Study	Risk factor	Study details	RR (95% CI)
Nafstad et al. 2004	NO_x	Within-city; men 40–49 years of age in Oslo, Norway (*n* = 16,209)	1.08[a] (1.06, 1.11) per 10 μg/m³
Jerrett et al. 2005	$PM_{2.5}$	Within-city, subset (Los Angeles, CA) of the ACS cohort (*n* = 22,905)	1.25[a] (0.99, 1.59) per 10 μg/m³
Jerrett et al. 2009	O_3	Between-cities; ACS cohort (*n* = 448,850)	1.008[a] (1.002, 1.013) per 10 μg/m³
WHO 2004	Physical inactivity	Meta-analysis of 23 studies from two continents (Western Europe, & North America. 12; total *n* = 327,604)	Insufficiently active[b]: 1.31 (1.21, 1.41) Inactive[b]: 1.47 (1.32, 1.56)

[a]Air pollution risk estimates used here were based on long-term cohort studies and chronic health effects. [b]Referent, > 150 min/week; insufficiently active, 1–150 min/week; inactive, 0 min/week.

GL14 Continued

(86–112 μg/m³; annual average of 1-hr daily maximums), and 22 μg/m³ for $PM_{2.5}$ (20–24 μg/m³; Table 2). Mean NO_2 exposures were below current ambient-air standards [U.S. EPA and California Environmental Protection Agency (CalEPA) standards, respectively: 100 and 57 μg/m³]. $PM_{2.5}$ exposures were approximately 1.5 and 2 times higher than U.S. EPA (15 μg/m³) and CalEPA (12 μg/m³) long-term standards (annual arithmetic mean), respectively (California Air Resources Board 2010).

Table 2. Descriptive statistics by neighborhood type [mean (IQR)].

Variable	All (*n* = 30,007)	Low walkability (*n* = 5,365)	High walkability (*n* = 3,549)
Age (years)	38 (21–56)	41 (23–58)	34 (20–47)
Nonwhite (%)	43	23	65
Male (%)	50	49	50
Income > $50,000 per year (%)	48	57	31
College or more (%)	48	52	40
NO_2 (μg/m³)[a]	85 (68–103)	67 (53–88)	108 (89–130)
O_3 (μg/m³)[a]	99 (86–112)	111 (97–124)	85 (82–92)
$PM_{2.5}$ (μg/m³)[a]	22 (20–24)	20 (18–23)	23 (22–24)
Physical activity (min/week)	77 (0–0)	88 (0–0)	102 (0–0)
Population density in Census tract (people/km²)[b]	22,400 (7,800–29,400)	3,100 (630–5,200)	53,500 (31,500–61,900)
Intersection density (1-km network buffer)[b]	57 (27–82)	11 (2–20)	109 (88–114)
Land use mix (1-km network buffer)[b]	0.37 (0.25–0.49)	0.13 (0–0.23)	0.59 (0.50–0.68)

All continuous variables in high-walkability neighborhoods have statistically significant differences (for all variables $p < 0.001$) compared with low-walkability neighborhoods (two-tailed *t*-test).
[a]Home-location annual-average concentrations. [b]Home-location annual average of daily 1-hr maximum concentrations.
[c]This land use variable was used to define walkability.

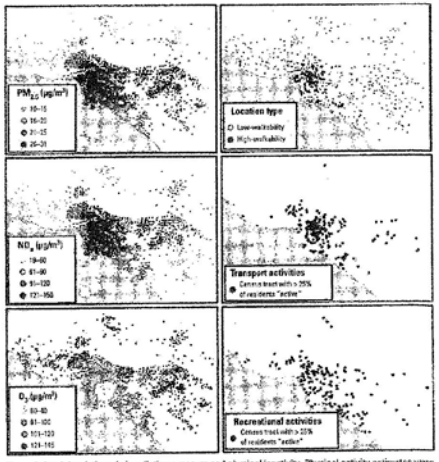


Figure 2. Spatial variation of air pollution exposure and physical inactivity. Physical activity estimates were derived from time–activity diaries, air pollution exposures were calculated from U.S. EPA monitoring data, and walkability was defined using publicly available land use variables. Icons for transport and recreational activities represent census tracts where > 25% of the survey respondents reported > 150 min/week of that activity type.

Self-reported physical activity levels averaged 77 min/week (IQR, 0–0 min/week; i.e., the 25th and 75th values are 0 min/week; Table 2). Most (83.5%) of the survey participants reported being inactive (0 min/week), 5.6% reported being insufficiently active (1–150 min/week), and 10.9% reported being active (> 150 min/week; physical activity recommendations; U.S. Department of Health and Human Services 1996). Activity levels were notably lower than national averages (U.S. averages: inactive, 29%; insufficiently active, 45%; active, 26%; WHO 2004). Sensitivity analysis 1 addresses this difference in activity levels.

NO_2 and $PM_{2.5}$ concentrations were highest near the city center and major roadways, whereas O_3 concentrations were higher in the outer-lying areas (Figure 2). Because of this spatial pattern, few locations experienced low exposure to all three pollutants. Spatial patterns for physical activity were dependent on the purpose of the activity; there was no discernable spatial pattern for recreational activities, but active transport was clustered near high-walkability neighborhoods (Figure 2).

Average per capita physical activity was 50% higher in high- than in low-walkability neighborhoods (102 vs. 68 min/week; Figure 3). The number of nonsedentary individuals (people with > 0 min/week physical activity) was two times higher in high- versus low-walkability neighborhoods (24.9% and 12.5%, respectively; $p < 0.001$). However, considering nonsedentary individuals only, average physical activity was 24% lower in high- than in low-walkability neighborhoods (410 vs. 543 min/week). This finding suggests that neighborhood type may have differing impacts on the number of people participating in physical activities, average physical activity among all individuals, and average physical activity among nonsedentary individuals.

The self-reported purpose of physical activity differs by neighborhood (Figure 3). For example, active transport accounts for about half of physical activity in the high-walkability neighborhoods but only 20% in low-walkability neighborhoods. Active transport is 3.6 times higher in high- versus low-walkability neighborhoods (a finding that partially corroborates our GIS estimates of walkability), whereas nontravel activity is similar (< 10% difference) in low- versus high-walkability neighborhoods. Activity level and purpose exhibited greater weekend/weekday differences in low-walkability areas than in high-walkability areas [see Supplemental Material, Table S2, Figure S4 (http://dx.doi.org/10.1289/ehp.1103806)].

Figure 4 shows estimated attributable IHD mortality rates for each neighborhood type

GL14 Continued

and risk factor. Physical inactivity was more strongly associated with IHD mortality (51 additional deaths/100,000/year overall) than were the other exposures, but IHD mortality attributable to physical inactivity was only slightly different between high- and low-walkability neighborhoods (7 fewer IHD deaths/100,000/year in high- vs. low-walkability). Conversely, overall estimated attributable IHD mortality due to exposure to $PM_{2.5}$ was smaller (30 deaths/100,000/year), but the difference between neighborhoods was slightly larger than for physical inactivity (9 more IHD deaths/100,000/year in high- vs. low-walkability). O_3 shows the reverse spatial pattern as $PM_{2.5}$ (i.e., O_3 exposure is higher in low-walkability neighborhoods, whereas $PM_{2.5}$ is lower) but a smaller difference in mortality between neighborhoods (3 fewer IHD deaths/100,000/year in high- vs. low-walkability). Attributable IHD mortality rates for NO_2 (represented by risk estimates for men 40–49 years of age; not shown in Figure 4) were 13 (28) IHD deaths/100,000/year for low- (high-) walkability neighborhoods. Attributable risk estimates for physical inactivity, $PM_{2.5}$, and O_3 showed similar patterns when neighborhoods were classified according to deciles of walkability scores [Supplemental Material, Figure S5 (http://dx.doi.org/10.1289/ehp.1103806)].

Sensitivity analysis 1: scaling method for minutes of physical activity. Results [see Supplemental Material, pp. 8–9 (http://dx.doi.org/10.1289/ehp.1103806)] indicate that our alternative assumptions reduce the variability in physical activity among neighborhoods. Specifically, the Monte Carlo simulation increases the share of nonsedentary individuals (subsequently reducing average risks from physical inactivity) but also yields reductions in estimated IHD mortality differences among neighborhoods. Our core conclusions are similar among the Monte Carlo simulations.

Sensitivity analysis 2: air pollution model. Central tendencies varied by pollutant and model; however, trends in the core conclusions (i.e., shifts in exposure and risk by neighborhood type) were similar where it was possible to compare [see Supplemental Material, pp. 9–10 (http://dx.doi.org/10.1289/ehp.1103806)]. In general, differences in estimated IHD mortality rates between high- and low-walkability neighborhoods were larger when using the alternate models; therefore, base-case results reported above may be conservative estimates (i.e., underestimates) of air pollution spatial variability.

Sensitivity analysis 3: physical activity dose–response. Our results did not change appreciably when using the linear dose–response curves [see Supplemental Material, pp. 10–11 (http://dx.doi.org/10.1289/ehp.1103806)].

We also estimated RRs according to neighborhood type (high- or low-walkability) within strata of age (0–25 years, 26–50 years, > 50 years) and according to income and ethnicity (high income (> $75,000) and white vs. low income (< $35,000) and nonwhite). The results reveal similar trends in risk differences between neighborhoods for each strata, suggesting that our results are robust to accounting for differences in income, ethnicity, and age. Details are in the Supplemental Material [pp. 11–14, Table S6 (http://dx.doi.org/10.1289/ehp.1103806)]. Prior literature further explores socioeconomic aspects of this topic (e.g., Ewing 2005; Frank et al. 2007; Sallis et al. 2009).

Discussion

Our analysis summarizes between-neighborhood variations in two risk factors (exposure to air pollution, physical inactivity) using a time–activity travel diary for one region. We found risks were differential when stratified by neighborhood walkability. Specifically, when comparing estimated IHD mortality rates among neighborhoods, differences attributable to physical inactivity were modest and comparable to differences attributable to individual air pollutants. Because of spatial patterns associated with each pollutant, urban residents were often highly exposed to at least one but not all pollutants (e.g., high exposure to O_3 in low-walkability neighborhoods or high exposure to $PM_{2.5}$ in high-walkability neighborhoods). This trade-off suggests that the net health impact of neighborhoods may depend in part on spatial patterns of air pollution.

Recent health comparisons between air pollution and exercise (Carlisle and Sharp 2001; de Hartog et al. 2010) emphasize the greater health importance of exercise relative to air pollution. This prior research considered only people who exercise (Carlisle and Sharp 2001; de Hartog et al. 2010); here, we consider the entire population—nonsedentary plus sedentary individuals. Only a subset of a given population is physically active, and only a subset of that physical activity is influenced by neighborhood design; here, the net result is that spatial differences in attributable IHD mortality risks are of similar magnitude for physical inactivity as for air pollution. Our results indicate a doubling in the share of nonsedentary people in high- versus low-walkability neighborhoods (24.9% vs. 12.5%); however, all individuals—inactive and active—experience changes in air pollution exposures. For this study population, physical activity rates were higher (and exercise-attributable IHD mortality rates lower) in high- than in low-walkability neighborhoods. However, because variations in air pollution risk are similar to variations in physical inactivity risks, when comparing high- versus low-walkability neighborhoods, health benefits from increased physical activity may be offset by health risks from air pollution exposure.

Our study uses self-reported rather than objectively measured physical activity. Previous studies that have used objectively-measured physical activity to investigate effects of urban form on physical activity (Table 3) have reported mixed results: two studies reported

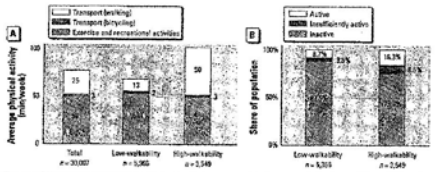


Figure 3. Differences among neighborhoods. (*A*) Average active transport (minutes walking and bicycling per person) and recreational activities. (*B*) Physical activity levels. The between-neighborhood difference in total physical activity is statistically significant ($p < 0.001$, two-tailed *t*-test).

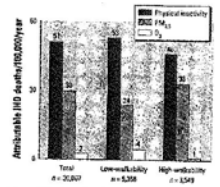


Figure 4. Estimated attributable IHD mortality rates for each risk factor and neighborhood type. Rates were calculated using means of individual RRs and prevalence of exposure within neighborhood type [referent, > 150 min/week of physical activity; 10th percentile of air pollution exposure (12.6 μg/m³ for $PM_{2.5}$, 39.8 μg/m³ for NO_2, and 80.3 μg/m³ for O_3)]. The overall incidence of IHD mortality in California is 191 deaths/100,000/year (CDC 2011).

GL14 Continued

GL14 Continued

Table 3. Comparison of results from studies using objective measures of physical activity with results from the present study.

Study	Location	Measure of physical activity	Measure of urban form	Core result
Sallis et al. 2009	Seattle, WA, and Baltimore, MD	Objective: 7-day accelerometer	Walkability (net residential density, intersection density, land use mix, retail floor area ratio)	41 min/week increase in physical activity between high- vs. low-walkability neighborhoods
Frank et al. 2005	Atlanta, GA	Objective: 2-day accelerometer	Walkability (net residential density, intersection density, land use mix)	Two-fold increase in meeting physical activity recommendations in high- vs. low-walkability neighborhoods
Forsyth et al. 2008	St. Paul, MN	Objective: 7-day accelerometer	Population density, block size (street pattern)	Significant increase in transport-related physical activity (high- vs. low-walkability neighborhoods) but no difference in total physical activity
Present study	South Coast Air Basin, CA	Self-report: one-day time activity diary	Walkability (population density, intersection density, land use mix)	34 min/week increase in physical activity between high- vs. low-walkability neighborhoods (2-fold increase in meeting physical activity recommendations)

differences in physical activity by neighborhood type (Frank et al. 2005; Sallis et al. 2009), and one indicated shifts in the purpose (transport vs. fitness) but not the amount of physical activity (Forsyth et al. 2008). These findings suggest that urban-scale differences in physical activity rates are similar between objectively measured physical activity and our self-reported measures of activity. For example, differences in per capita physical activity between high- and low-walkability neighborhoods in Seattle, Washington, and Baltimore, Maryland, were similar to differences in our southern California population [41 min/week (Seattle, Baltimore) versus 34 min/week (southern California) (Sallis et al. 2009)].

Our study limitations include those associated with travel surveys and self-reported information in general. For example, travel surveys typically undercount trips by all modes (Bricka and Bhat 2006), affecting estimates of travel time (Wolf et al. 2003). The SCAG survey suggests that vehicle undercount rates may approach 20–25% but gives little information regarding nonmotorized trips (SCAG 2004). Undercount rates may be differential by trip length (SCAG 2004), mode, or neighborhood. Comparisons with studies using objectively measured physical activity (see preceding paragraph) suggest that our core findings are robust to trip undercounting and other problems with self-reported travel data.

Our work is motivated by the goal of understanding and designing clean, healthy, sustainable cities (Giles et al. 2011). Our investigation explores only one location (Los Angeles), one health outcome (IHD), one cohort, a small number of pollutants (NO_x, $PM_{2.5}$, O_3), and physical inactivity. Clearly, further analyses incorporating other risk factors (e.g., noise, transport injury) linked to the built environment are warranted. Interaction between physical activity and air pollution may vary on an even smaller scale than we have investigated in the present study (i.e., within neighborhoods). Future analyses could use age-specific risks of IHD mortality for air pollution and physical inactivity. Our analysis is descriptive (i.e., cross-sectional) in nature; more research is needed to explore causality between urban form and health risks (especially for physical activity, because ambient air pollution exposure is largely determined by geographical location).

Despite these limitations, our results are relevant to health officials, sustainability scientists, and urban planners. To our knowledge, ours is the first analysis that directly compares health risks for both air pollution and physical inactivity among neighborhoods based on activity patterns for a random sample of residents in an urban area, and thus is the first to quantify relationships between urban form and the health impacts of physical activity and air pollution. We found that attributes of the built environment were associated with both air pollution exposure and physical inactivity. These results emphasize that to be health protective, neighborhoods designed to decrease risks from one factor must avoid unintentionally increasing risks from other factors.

Conclusion

We compared the health impacts attributable to air pollution and physical inactivity among neighborhoods for one cohort (~ 30,000 individuals in Southern California). A larger proportion of our Southern California study population was classified as nonsedentary in high- versus low-walkability neighborhoods (25% vs. 13%). However, because only a small share of the total population was classified as physically active, we estimated only moderate differences in IHD mortality rates attributable to physical inactivity between neighborhood types. Spatial patterns of estimated attributable IHD mortality rates varied by pollutant: estimated mortality due to increased $PM_{2.5}$ and NO_x were greater in high- than in low-walkability neighborhoods, whereas estimated IHD mortality due to increased O_3 was greater in low- than in high-walkability neighborhoods. In general, differences in estimated IHD mortality between neighborhoods were comparable for exposure to air pollutants and physical inactivity. Our results suggest complex within-urban spatial trade-offs in health risks associated with air pollution and physical inactivity. Efforts to design healthy neighborhoods should account for many factors, including air pollution and physical inactivity, and not address one concern at the expense of others.

References

Andersen L, Schnohr P, Schroll M, Hein HO. 2000. All-cause mortality associated with physical activity during leisure time, work, sports, and cycling to work. Arch Intern Med 160:1621–1628.

Baker D, Nieuwenhuijsen M, eds. 2008. Environmental Epidemiology: Study Methods and Application. New York:Oxford University Press, 326–328.

Bricka S, Bhat C. 2006. Comparative analysis of global positioning system-based and travel survey-based data. Transport Res Rec 1972(1):9–20.

Brunekreef B, Holgate ST. 2002. Air pollution and health. Lancet 360(9341):1233–1242.

California Air Resources Board. 2010. Ambient Air Quality Standards. Available: http://www.arb.ca.gov/research/aaqs/aaqs2.pdf [accessed 10 November 2010].

Carlisle AJ, Sharp NCC. 2001. Exercise and outdoor ambient air pollution. Br J Sports Med 35(4):214–222.

CDC (Centers for Disease Control and Prevention). 2009. Deaths: Final Data for 2005. Natl Vital Stat Rep 57(14):1–135. Available: http://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57_14.pdf [accessed 10 November 2010].

CDC (Centers for Disease Control and Prevention). 2011. Health Data Interactive. Available: http://www.cdc.gov/nchs/hdi.htm [accessed 9 February 2011].

Colditz GA, Cannuscio CC, Frazier AL. 1997. Physical activity and reduced risk of colon cancer: implications for prevention. Cancer Causes Control 8(4):649–667.

de Hartog JJ, Boogaard H, Nijland H, Hoek G. 2010. Do the health benefits of cycling outweigh the risks? Environ Health Perspect 118:1109–1116.

de Nazelle A, Rodriguez DA, Crawford-Brown D. 2009. The built environment and health: impacts of pedestrian-friendly designs on air pollution exposure. Sci Total Environ 407(8):2525–2535.

Ewing R. 2005. Can the physical environment determine physical activity levels? Exerc Sport Sci Rev 33(2):69–75.

Ewing R, Cervero R. 2001. Travel and the built environment: a synthesis. Transport Res Rec 1780:87–114.

Ewing R, Schmid T, Killingsworth R, Zlot A, Raudenbush S. 2003. Relationship between urban sprawl and physical activity, obesity, and morbidity. Am J Health Promot 18(1):47–57.

Forsyth A, Hearst M, Oakes JM, Schmitz KH. 2008. Design and destinations: factors influencing walking and total physical activity. Urban Stud 45(9):1973–1996.

Frank LD, Andresen MA, Schmid TL. 2004. Obesity relationships with community design, physical activity, and time spent in cars. Am J Prev Med 27(2):87–96.

Frank LD, Saelens BE, Powell KE, Chapman JE. 2007. Stepping towards causation: do built environments or neighborhood and travel preferences explain physical activity, driving, and obesity? Soc Sci Med 65(9):1898–1914.

Frank LD, Schmid TL, Sallis JF, Chapman J, Saelens BE. 2005. Linking objectively measured physical activity with objectively measured urban form. Am J Prev Med 28(2):117–125.

Gent JF, Triche EW, Holford TR, Belanger K, Bracken MB, Beckett WS, et al. 2003. Association of low-level ozone and fine particles with respiratory symptoms in children with asthma. JAMA 290(14):1859–1867.

Giles LV, Barn P, Künzli N, Romieu I, Mittleman MA, van Eeden S, et al. 2011. From good intentions to proven interventions: effectiveness of actions to reduce the health impacts of air pollution. Environ Health Perspect 119:29–36.

Grabow ML, Spak SN, Holloway T, Stone B Jr, Mednick AC, Patz JA. 2011. Air quality and exercise-related health benefits from reduced car travel in the midwestern United States. Environ Health Perspect 120:68–76.

Hamer M, Chida Y. 2008. Active commuting and cardiovascular risk: a meta-analytic review. Prev Med 46(1):9–13.

Handy SL, Boarnet MG, Ewing R, Killingsworth RE. 2002. How the built environment affects physical activity: views from urban planning. Am J Prev Med 23 (2 suppl):64–73.

Health Effects Institute. 2009. Traffic-Related Air Pollution: A Critical Review of the Literature on Emissions, Exposure, and Health Effects. Available: http://pubs.healtheffects.org/view.php?id=334 [accessed 9 September 2010].

Holtzclaw J, Clear R, Dittmar H, Goldstein D, Haas P. 2002. Location efficiency: neighborhood and socioeconomic characteristics determine auto ownership and use—studies in Chicago, Los Angeles, and San Francisco. Transport Plan Technol 25(1):1–27.

Jerrett M, Burnett RT, Ma R, Pope CA, Krewski D, Newbold KB, et al. 2005. Spatial analysis of air pollution and mortality in Los Angeles. Epidemiology 16(6):727–736.

Jerrett M, Burnett RT, Pope CA, Ito K, Thurston G, Krewski D, et al. 2009. Long-term ozone exposure and mortality. N Engl J Med 360(11):1085–1095.

Kelley D, Goodpaster B. 2001. Effects of exercise on glucose homeostasis in type 2 diabetes mellitus. Med Sci Sport Exer 33(6 suppl):S495–S501.

Kohl KW. 2001. Physical activity and cardiovascular disease: evidence for a dose response. Med Sci Sport Exer 33(6 suppl):S472–S483.

Marshall JD. 2008. Energy-efficient urban form. Environ Sci Technol 42(9):3133–3137.

Marshall JD, Brauer M, Frank LD. 2009. Healthy neighborhoods: walkability and air pollution. Environ Health Perspect 117:1752–1759.

Marshall JD, Granvold PW, Hoats AS, McKone TE, Deakin E, Nazaroff WW. 2006. Inhalation intake of ambient air pollution in California's South Coast Air Basin. Atmos Environ 40(23):4381–4392.

Marshall JD, McKone TE, Deakin EA, Nazaroff WW. 2005. Inhalation of motor vehicle emissions: effects of urban population and land area. Atmos Environ 39(2):283–295.

Marshall JD, Nethery E, Brauer M. 2008. Within-urban variability in ambient air pollution: comparison of estimation methods. Atmos Environ 42(6):1359–1369.

Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, et al. 2007. Long-term exposure to air pollution and incidence of cardiovascular events in women. New Engl J Med 356(5):447–458.

Morabia A, Mirer FE, Amstislavski TM, Eisl HM, Werbe-Fuentes J, Gorczynski J, et al. 2010. Potential health impact of switching from car to public transportation when commuting to work. Am J Public Health 100(12):2388–2391.

Nafstad P, Haheim LL, Wisloff T, Gram F, Oftedal B, Holme I, et al. 2004. Urban air pollution and mortality in a cohort of Norwegian men. Environ Health Perspect 112:610–615.

Novotny EV, Bechle M, Millet DB, Marshall JD. 2011. National satellite-based land-use regression: NO_2 in the United States. Environ Sci Technol 45(10):4407–4414.

Pope CA, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, et al. 2002. Lung cancer, cardiopulmonary, and long-term exposure to fine particulate air pollution. JAMA 287(9):1132–1141.

Pope CA, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, et al. 2004. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. Circulation 109(1):71–77.

Pope CA, Dockery DW. 2006. Health effect of fine particulate air pollution: lines that connect. J Air Waste Manag Assoc 56(6):709–742.

Saelens BE, Sallis JF, Black JB, Chen D. 2003a. Neighborhood-based differences in physical activity: an environmental scale evaluation. Am J Public Health 93(9):1552–1558.

Saelens BE, Sallis JF, Frank LD. 2003b. Environmental correlates of walking and cycling: findings from the transportation, urban design, and planning literatures. Ann Behav Med 25(2):80–91.

Sallis JF, Saelens BE, Frank LD, Conway TL, Slymen DJ, Cain KL, et al. 2009. Neighborhood built environment and income: examining multiple health outcomes. Soc Sci Med 68(7):1285–1293.

SCAG (Southern California Association of Governments). 2003. Post Census Regional Household Travel Survey: Data User's Manual. Austin, TX:NuStats. Available: http://www.scag.ca.gov/travelsurvey/pdf/TravelSurveyData_UsersManual.pdf [accessed 10 May 2010].

SCAG (Southern California Association of Governments). 2004. Year-2000 Post Census Regional Household Study: GPS Study Final Report. Los Angeles, CA:NuStats.

SCAG (Southern California Association of Governments). 2010. Planning Data. Available: http://www.scag.ca.gov/planning.htm [accessed 15 August 2010].

U.S. Census Bureau. 2000. TIGER Products: Topologically Integrated Geographic Encoding and Referencing System. Available: http://www.census.gov/geo/www/tiger/ [accessed 7 July 2010].

U.S. Department of Health and Human Services. 1996. Physical Activity and Health: A Report of the Surgeon General. Atlanta, GA:Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, President's Council on Physical Fitness and Sports.

U.S. EPA (U.S. Environmental Protection Agency). 2010. Technology Transfer Network (TTN): Air Quality System (AQS) Data Mart [database]. Available: http://www.epa.gov/ttn/airs/aqsdatamart [accessed 27 April 2010].

Verloop J, Rookus MA, van der Kooy K, van Leeuwen FE. 2000. Physical activity and breast cancer risk in women aged 20–54 years. J Natl Cancer Inst 92(2):128–135.

WHO (World Health Organization). 2004. Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors. Available: http://www.who.int/healthinfo/global_burden_disease/cra/en/index.html [accessed 10 May 2010].

WHO (World Health Organization). 2009. Global Health Risks: Mortality and Burden of Disease Attributable to Selected Major Risks. Available: http://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_full.pdf [accessed 10 May 2010].

Wolf J, Oliveira M, Thompson M. 2003. The impact of trip underreporting on VMT and travel time estimates: preliminary findings from the California statewide household travel survey GPS study. In: Proceeding from the Transportation Research Board 82nd Annual Meeting [preprint CD-ROM]. Washington, DC:Transportation Research Board, National Research Council.

Wong C, Ou C, Thach T, Chau Y, Chan K, Ho SY, et al. 2007. Does regular exercise protect against air pollution-associated mortality? Prev Med 44(5):386–392.

Woodcock J, Edwards P, Tonne C, Armstrong BG, Ashiru O, Banister D, et al. 2009. Public health benefits of strategies to reduce greenhouse-gas emissions: urban land transport. Lancet 374(9705):1930–1943.

Zheng H, Orsini N, Amin J, Wolk A, Nguyen VTT, Ehrlich F. 2009. Quantifying the dose–response of walking in reducing coronary heart disease risk: meta-analysis. Eur J Epidemiol 24(4):181–192.

GL14 Continued

Attachment G

Brugge, Doug et al.
Near Highway Pollutants in Motor Vehicle Exhaust: A Review
of Epidemiologic Evidence of Cardiac and Pulmonary Health Risks
Environmental Health
August 9, 2007

GL14 Continued

This page intentionally left blank.

GL14 Continued

Environmental Health

BioMed Central

Review

Open Access

Near-highway pollutants in motor vehicle exhaust: A review of epidemiologic evidence of cardiac and pulmonary health risks

Doug Brugge*[1], John L Durant[2] and Christine Rioux[3]

Address: [1]Tufts Community Research Center, Tufts University School of Medicine, Boston, MA, USA, [2]Department of Civil and Environmental Engineering, Tufts University, Medford, MA 02155, USA and [3]Interdisciplinary PhD Program, Tufts University, Medford, MA 02155, USA

Email: Doug Brugge* - dbrugge@aol.com; John L Durant - john.durant@tufts.edu; Christine Rioux - Christine.rioux@tufts.edu

* Corresponding author

Published: 9 August 2007

Environmental Health 2007, **6**:23 doi:10.1186/1476-069X-6-23

Received: 2 January 2007
Accepted: 9 August 2007

This article is available from: http://www.ehjournal.net/content/6/1/23

Abstract

There is growing evidence of a distinct set of freshly-emitted air pollutants downwind from major highways, motorways, and freeways that include elevated levels of ultrafine particulates (UFP), black carbon (BC), oxides of nitrogen (NOx), and carbon monoxide (CO). People living or otherwise spending substantial time within about 200 m of highways are exposed to these pollutants more so than persons living at a greater distance, even compared to living on busy urban streets. Evidence of the health hazards of these pollutants arises from studies that assess proximity to highways, actual exposure to the pollutants, or both. Taken as a whole, the health studies show elevated risk for development of asthma and reduced lung function in children who live near major highways. Studies of particulate matter (PM) that show associations with cardiac and pulmonary mortality also appear to indicate increasing risk as smaller geographic areas are studied, suggesting localized sources that likely include major highways. Although less work has tested the association between lung cancer and highways, the existing studies suggest an association as well. While the evidence is substantial for a link between near-highway exposures and adverse health outcomes, considerable work remains to understand the exact nature and magnitude of the risks.

Background

Approximately 11% of US households are located within 100 meters of 4-lane highways [estimated using: [1,2]]. While it is clear that automobiles are significant sources of air pollution, the exposure of near-highway residents to pollutants in automobile exhaust has only recently begun to be characterized. There are two main reasons for this: (A) federal and state air monitoring programs are typically set up to measure pollutants at the regional, not local scale; and (B) regional monitoring stations typically do not measure all of the types of pollutants that are elevated next to highways. It is, therefore, critical to ask what is known about near-highway exposures and their possible health consequences.

Here we review studies describing measurement of near-highway air pollutants, and epidemiologic studies of cardiac and pulmonary outcomes as they relate to exposure to these pollutants and/or proximity to highways. Although some studies suggest that other health impacts are also important (e.g., birth outcomes), we feel that the case for these health effects are less well developed scientifically and do not have the same potential to drive public policy at this time. We did not seek to fully integrate the relevant cellular biology and toxicological literature, except for a few key references, because they are so vast by themselves.

GL14 Continued

We started with studies that we knew well and also searched the engineering and health literature on Medline. We were able to find some earlier epidemiologic studies based on citations in more recent articles. We include some studies that assessed motor vehicle-related pollutants at central site monitors (i.e., that did not measure highway proximity or traffic) because we feel that they add to the plausibility of the associations seen in other studies. The relative emphasis given to studies was based on our appraisal of the rigor of their methodology and the significance of their findings. We conclude with a summary and with recommendations for policy and further research.

Motor vehicle pollution

It is well known that motor vehicle exhaust is a significant source of air pollution. The most widely reported pollutants in vehicular exhaust include carbon monoxide, nitrogen and sulfur oxides, unburned hydrocarbons (from fuel and crankcase oil), particulate matter, polycyclic aromatic hydrocarbons, and other organic compounds that derive from combustion [3-5]. While much attention has focused on the transport and transformation of these pollutants in ambient air – particularly in areas where both ambient pollutant concentrations and human exposures are elevated (e.g., congested city centers, tunnels, and urban canyons created by tall buildings), less attention has been given to measuring pollutants and exposures near heavily-trafficked highways. Several lines of evidence now suggest that steep gradients of certain pollutants exist next to heavily traveled highways and that living within these elevated pollution zones can have detrimental effects on human health.

It should be noted that many different types of highways have been studied, ranging from California "freeways" (defined as multi-lane, high-speed roadways with restricted access) to four-lane (two in each direction), variable-speed roadways with unrestricted access. There is considerable variation in the literature in defining highways and we choose to include studies in our review that used a broad range of definitions (see Table 1).

It should also be noted that there may be significant heterogeneity in the types and amounts of vehicles using highways. The typical vehicle fleet in the US is composed of passenger cars, sports utility vehicles, motorcycles, pickup trucks, vans, buses, and small, medium, and large trucks. The composition and size of a fleet on a given highway may vary depending on the time of day, day of the week, and use restrictions for certain classes of vehicles. Fleets may also vary in the average age and state of repair of vehicles, the fractions of vehicles that burn diesel and gasoline, and the fraction of vehicles that have catalytic converters. These factors will influence the kinds and amounts of pollutants in tailpipe emissions. Similarly, driving conditions, fuel chemistry, and meteorology can also significantly impact emissions rates as well as the kinds and concentrations of pollutants present in the near-highway environment. These factors have rarely been taken into consideration in health outcome studies of near-highway exposure.

Based on our review of the literature, the pollutants that have most consistently been reported at elevated levels near highways include ultrafine particles (UFP), black carbon (BC), nitrogen oxides (NOx), and carbon monoxide (CO). In addition, $PM_{2.5}$ and PM_{10} were measured in many of the epidemiologic studies we reviewed. UFP are defined as particles having an aerodynamic diameter in the range of 0.005 to 0.1 microns (um). UFP form by condensation of hot vapors in tailpipe emissions, and can grow in size by coagulation. $PM_{2.5}$ and PM_{10} refer to particulate matter with aerodynamic diameters of 2.5 and 10 um, respectively. BC (or "soot carbon") is an impure form of elemental carbon that has a graphite-like structure. It is the major light-absorbing component of combustion aerosols. These various constituents can be measured in real time or near-real time using particle counters (UFP) and analyzers that measure light absorption (BC and CO), chemiluminescence (NOx), and weight ($PM_{2.5}$ and PM_{10}). Because UFP, NO_x, BC, and CO derive from a common source – vehicular emissions – they are typically highly inter-correlated.

Air pollutant gradients near highways

Several recent studies have shown that sharp pollutant gradients exist near highways. Shi et al. [6] measured UFP number concentration and size distribution along a roadway-to-urban-background transect in Birmingham (UK), and found that particle number concentrations decreased nearly 5-fold within 30 m of a major roadway (>30,000 veh/d). Similar observations were made by Zhu et al. [7,8] in Los Angeles. Zhu et al. measured wind speed and direction, traffic volume, UFP number concentration and size distribution as well as BC and CO along transects downwind of a highway that is dominated by gasoline vehicles (Freeway 405; 13,900 vehicles per hour; veh/h) and a highway that carries a high percentage of diesel vehicles (Freeway 710; 12,180 veh/h). Relative concentrations of CO, BC, and total particle number concentration decreased exponentially between 17 and 150 m downwind from the highways, while at 300 m UFP number concentrations were the same as at upwind sites. An increase in the relative concentrations of larger particles and concomitant decrease in smaller particles was also observed along the transects (see Figure 1). Similar observations were made by Zhang et al. [9] who demonstrated "road-to-ambient" evolution of particle number distributions near highways 405 and 710 in both winter and sum-

GL14 Continued

Table 1: Summary of near-highway pollution gradients

Citation	Location	Highway traffic intensity[a]	Pollutants measured[b]	Observed Pollution Gradients
Shi et al. 1999 (6)	Birmingham, UK	30,000 veh/d	UFP + FP ($10–10^4$ nm)	2–100 m [c]
Zhu et al. 2002 (8)	Los Angeles; Freeway 710	12,100 veh/h	UFP, CO, BC	17–300 m [c]
Zhu et al. 2002 (7)	Los Angeles; Freeway 405	13,900 veh/h	UFP, CO, BC	30–300 m [c]
Hitchins et al. 2002 (11)	Brisbane (Austr.)	2,130–3,400 veh/h	UFP + FP ($15.2 < 10^4$ nm), $PM_{2.5}$	15–375 m [c]
Fischer et al. 2000 (13)	Amsterdam	<3,000–30,974 veh/d	$PM_{2.5}$, PM_{10}, PPAH, VOCs	NA
Roorda-Knape et al. 1998 (14)	Netherlands	80,000–152,000 veh/d	$PM_{2.5}$, PM_{10}, BC, VOCs, NO_2	15–330 m [c]
Janssen et al. 2001 (15)	Netherlands	40,000–170,000 veh/d	$PM_{2.5}$, VOCs, NO_2	< 400 m [c]
Morawska et al. 1999 (12)	Brisbane (Austr.)	NA	UFP	10–210 m [c]

[a]As defined in article cited (veh/d = vehicles per day; veh/h = vehicles per hour).
[b]UFP = ultrafine particles; FP = fine particles; $PM_{2.5}$ = particles with aerodynamic diameter ≤ 2.5 um; PM_{10} = particles with aerodynamic diameter ≤ 10 um; BC = black carbon; PPAH = particle-bound polycyclic aromatic hydrocarbons; VOCs = volatile organic compounds
[c]Pollutant measurements were made along a transect away from the highway
NA = not applicable; measurements were not made.

mer. Zhang et al. observed that between 30–90 m downwind of the highways, particles grew larger than 0.01 um due to condensation, while at distances >90 m, there was both continued particle growth (to >0.1 um) as well as particle shrinkage to <0.01 um due to evaporation. Because condensation, evaporation, and dilution alter size distribution and particle composition, freshly-emitted UFP near highways may differ in chemical composition from UFP that has undergone atmospheric transformation during transport to downwind locations [10].

Two studies in Brisbane (Australia) highlight the importance of wind speed and direction as well as contributions of pollutants from nearby roadways in tracking highway-generated pollutant gradients. Hitchins et al. [11] measured the mass concentrations of 0.1–10 um particles as well as total particle number concentration and size distribution for 0.015–0.7 um particles near highways (2,130–3,400 veh/h). Hitchens et al. observed that the distance from highways at which number and mass concentrations decreased by 50% varied from 100 to 375 m depending on the wind speed and direction. Morawska et al. [12] measured the changes in UFP number concentrations along horizontal and vertical transects near highways to distinguish highway and normal street traffic contributions. It was observed that UFP number concentrations were highest <15 m from highways, while 15–200 m from highways there was no significant difference in UFP number concentrations along either horizontal or vertical transects – presumably due to mixing of highway pollutants with emissions from traffic on nearby, local roadways.

In addition to UFP, other pollutants – such as $PM_{2.5}$, PM_{10}, NO_2 (nitrogen dioxide), VOCs (volatile organic compounds), and particle-bound polycyclic aromatic hydrocarbons (PPAH) – have been studied in relation to heavily-trafficked roadways. Fischer et al. [13] measured $PM_{2.5}$, PM_{10}, PPAH, and VOC concentrations outside and inside homes on streets with high and low traffic volumes in Amsterdam (<3,000–30,974 veh/d). In this study, PPAH and VOCs were measured using methods based on gas chromatography. Fischer et al. found that while $PM_{2.5}$ and PM_{10} mass concentrations were not specific indicators of traffic-related air pollution, PPAH and VOC levels were ~2-fold higher both indoor and outdoor in high traffic areas compared to low traffic areas. Roorda-Knape et al [14] measured $PM_{2.5}$, PM_{10}, black smoke (which is similar to BC), NO_2, and benzene in residential areas <300 m from highways (80,000–152,000 veh/d) in the Netherlands. Black smoke was measured by a reflectance-based method using filtered particles; benzene was measured using a method based on gas chromatography. Roorda-Knape et al reported that outdoor concentrations of black smoke and NO_2 decreased with distance from highways, while $PM_{2.5}$, PM_{10}, and benzene concentrations did not change with distance. In addition, Roorda-Knape et al. found that indoor black smoke concentrations were correlated with truck traffic, and NO_2 was correlated with both traffic volume and distance from highways. Janssen et al. [15] studied $PM_{2.5}$, PM_{10}, benzene, and black smoke in 24 schools in the Netherlands and found that $PM_{2.5}$ and black smoke increased with truck traffic and decreased with distance from highways (40,000–170,000 veh/d).

In summary, the literature shows that UFP, BC, CO and NOx are elevated near highways (>30,000 veh/d), and that other pollutants including VOCs and PPAHs may also be elevated. Thus, people living within about 30 m of highways are likely to receive much higher exposure to

GL14 Continued

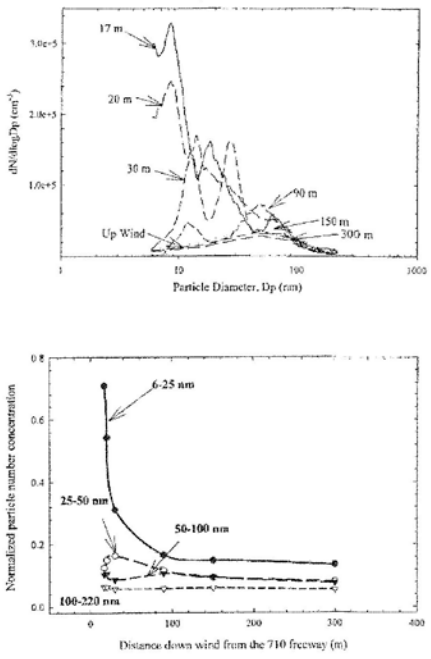


Figure 1
Ultrafine particle size distribution (top panel) and normalized particle number concentration for different size ranges (bottom panel) as a function of distance from a highway in Los Angeles. From Zhu et al. (8). Reprinted with permission from Elsevier.

GL14 Continued

traffic-related air pollutants compared to residents living >200 m (+/- 50 m) from highways.

Cardiovascular health and traffic-related pollution

Results from clinical, epidemiological, and animal studies are converging to indicate that short-term and long-term exposures to traffic-related pollution, especially particulates, have adverse cardiovascular effects [16-18]. Most of these studies have focused on, and/or demonstrated the strongest associations between cardiovascular health outcomes and particulates by weight or number concentrations [19-21] though CO, SO_2, NO_2, and BC have also been examined. BC has been shown to be associated with decreases in heart rate variability (HRV) [22,23] and black smoke and NO_2 shown to be associated with cardiopulmonary mortality [24].

Short-term exposure to fine particulate pollution exacerbates existing pulmonary and cardiovascular disease and long-term repeated exposures increases the risk of cardiovascular disease and death [25,26].

Though not focused on near-highway pollution, two large prospective cohort studies, the Six-Cities Study [27] and the American Cancer Society (ACS) Study [28] provided the groundwork for later research on fine particulates and cardiovascular disease. Both of these studies found associations between increased levels of exposure to ambient PM and sulfate air pollution recorded at central city monitors and annual average mortality from cardiopulmonary disease, which at the time combined cardiovascular and pulmonary disease other than lung cancer. The Six-Cities Study examined $PM_{2.5}$ and $PM_{10/15}$. The ACS study examined $PM_{2.5}$. Relative risk ratios of mortality from cardiopulmonary disease comparing locations with the highest and lowest fine particle concentrations (which had differences of 24.5 and 18.6 ug/m^3 respectively) were 1.37 (1.11, 1.68) and 1.31 (1.17, 1.46) in the Six Cities and ACS studies, respectively. These analyses controlled for many confounders, including smoking and gas stoves but not other housing conditions or time spent at home. The studies were subject to intensive replication, validation, and reanalysis that confirmed the original findings. $PM_{2.5}$ generally declined following implementation of new US Environmental Protection Agency standards in 1997 [17,29], yet since that time studies have shown elevated health risks due to long-term exposures to the 1997 PM threshold concentrations [29,30].

Much of the epidemiological research has focused on assessing the early physiological responses to short-term fluctuations in air pollution in order to understand how these exposures may alter cardiovascular risk profiles and exacerbate cardiovascular disease [31]. Heart rate variability, a risk factor for future cardiovascular outcomes, is altered by traffic-related pollutants particularly in older people and people with heart disease [22,23,32]. With decreased heart rate variability as the adverse outcome, negative associations between HRV and particulates were strongest for the smallest size fraction studied [33] (PM0.3–1.0); [34] (PM0.02–1). In two studies that included other pollutants, black carbon, an indicator of traffic particles, also elicited a strong association with both time and frequency domain HRV variables; associations were also strong for PM2.5 for both time and frequency HRV variables in the Adar et al study [23]; this and subsequent near highway studies are summarized in Table 2], however, PM2.5 was not associated with frequency domain variables in the Schwartz et al. study [22].

Several studies show that exposure to PM varies spatially within a city [35-37], and finer spatial analyses show higher risks to individuals living in close proximity to heavily trafficked roads [18,37]. A 2007 paper from the Woman's' Health Initiative used data from 573 $PM_{2.5}$ monitors to follow over 65,000 women prospectively. They reported very high hazard ratios for cardiovascular events (1.76; 95% CI, 1.25 to 2.47) possibly due to the fine grain of exposure monitoring [18]. In contrast, studies that relied on central monitors [27,28] or interpolations from central monitors to highways are prone to exposure misclassification because individuals living close to highways will have a higher exposure than the general area. A possible concern with this interpretation is that social gradients may also situate poorer neighborhoods with potentially more susceptible populations closer to highways [38-40].

At a finer grain, Hoek et al. [24] estimated home exposure to nitrogen dioxide (NO_2) and black smoke for about 5,000 participants in the Netherlands Cohort Study on Diet and Cancer. Modeled exposure took into consideration proximity to freeways and main roads (100 m and 50 m, respectively). Cardiopulmonary mortality was associated with both modeled levels of pollutants and living near a major road with associations less strong for background levels of both pollutants. A case-control study [41], found a 5% increase in acute myocardial infarction associated with living within 100 m of major roadways. A recent analysis of cohort data found that traffic density was a predictor of mortality more so than was ambient air pollution [42]. There is a need for studies that assess exposure at these scales, e.g., immediate vicinity of highways, to test whether cardiac risk increases still more at even smaller scales.

Although we cannot review it in full here, we note that evidence beyond the epidemiological literature support the contention that $PM_{2.5}$ and UFP (a sub-fraction of $PM_{2.5}$) have adverse cardiovascular effects [16,17]. $PM_{2.5}$ appears

GL14 Continued

Table 2: Summary of near-highway health effects studies

Citation	Location	Highway traffic intensity[a]	Pollutants measured[b]	Distance from highway	Health Outcomes	Statistical association[c]
Schwartz et al. 2005 (22)	Boston	NA	$PM_{2.5}$, BC, CO	NA	Heart rate variability	Decreases in measures of heart rate variability
Adar et al. 2007 (23)	St. Louis, Missouri	NA	$PM_{2.5}$, BC, UFP	On highway in buses	Heart rate variability	Decreases in measures of heart rate variability
Hoek et al. 2002 (24)	Netherlands	NA	BC, NO_2	Continuous [d]	Cardio-pulmonary mortality, lung cancer	1.41 OR for living near road
Tonne et al. 2007 (41)	Worchester, Mass.	NA	$PM_{2.5}$	Continuous [d]	Acute myocardial infarction (AMI)	5% increase in odds of AMI
Venn et al. 2001 (49)	Nottingham, UK	NA	NA	Continuous [d]	Wheezing in children	1.68 OR for living w/ in 150 m of road
Nicolai et al. 2003 (50)	Munich, Germany	>30,000 veh/d	Soot, benzene, NO_2	Traffic counts within 50 m of house	Asthma, respiratory symptoms, allergy	1.79 OR for asthma and high traffic volume
Gauderman et al. 2005 (65)	Southern California		NO_2	Continuous [d]	Asthma, respiratory symptoms	Increased asthma closer to freeways
McConnell et al. 2006 (51)	Southern California	NA	NA	Continuous [d]	Asthma	Large risk for children living w/in 75 m of road
Ryan, et al. 2007 (59)	Cincinnati, Ohio	> 8,000 trucks/d	PM2.5	400 m	Wheezing in children	NA
Kim et al. 2004 (60)	San Francisco	90,000 – 210,000 veh/d	PM, BC, NO_x	School sites	Childhood asthma	1.07 OR for high levels of NO_2
Wjst et al. 1993 (68)	Munich, Germany	7,000–125,000 veh/d	NO_x, CO	School sites	Asthma, bronchitis	Several statistical associations found
Brunekreef et al. 1997 (69)	Netherlands	99,000 – 152,000 veh/d	PM_{10}, NO_2	Continuous [d]	Lung function	Decreased FEV with proximity to high truck traffic
Janssen et al. 2003 (74)	Netherlands	30,000–135,000 veh/d	$PM_{2.5}$, NO_2, benzene	< 400 m [e]	Lung function, respiratory symptoms	No association with lung function
Peters et al. 1999 (82)	Southern California	NA	PM_{10}, NO_2	NA	Asthma, bronchitis, cough, wheeze	1.54 OR of wheeze for boys with exposure to NO_2
Brauer et al. 2007 (67)	Netherlands	Highways and streets	$PM_{2.5}$, NO_2, soot	Modeled exposure	Asthma, allergy, bronchitis, respiratory symptoms	Strongest association was with food allergies
Visser et al. 2004 (71)	Amsterdam	> 10,000 veh/d	NA	NA	Cancer	Multiple associations
Vineis et al. 2006 (87)	10 European countries	NA	PM_{10}, NO_2, SO_2	NA	Cancer	1.46 OR near heavy traffic, 1.30 OR for high exposure to NO_2
Gauderman et al. 2007 (73)	Southern California	NA	PM_{10}, NO_2	Continuous[f]	Lung function	Decreased FEV for those living near freeway

[a]As defined in article cited (veh/d = vehicles per day; veh/h = vehicles per hour).
[b]UFP = ultrafine particles; FP = fine particles; $PM_{2.5}$ = particles with aerodynamic diameter ≤ 2.5 um; PM_{10} = particles with aerodynamic diameter ≤ 10 um; BC = black carbon; PPAH = particle-bound polycyclic aromatic hydrocarbons; VOCs = volatile organic compounds
[c]Pollutant measurements were made along a transect away from the highway
[d]Proximity of each participant to a major road was calculated using GIS software
[e]Statistical association between proximity to highway or exposure to traffic-generated pollutants and measured health outcomes
NA = not applicable; measurements were not made.

to be a risk factor for cardiovascular disease via mechanisms that likely include pulmonary and systemic inflammation, accelerated atherosclerosis and altered cardiac autonomic function [17,22,43-46]. Uptake of particles or particle constituents in the blood can affect the autonomic control of the heart and circulatory system. Black smoke, a large proportion of which is derived from mobile source emissions [30], has a high pulmonary deposition efficiency, and due to their surface area-to-volume ratios can carry relatively more adsorbed and condensed toxic air pollutants (e.g., PPAH) compared to larger particles [17,47,48]. Based on high particle numbers, high lung deposition efficiency and surface chemistry, UFP may provide a greater potential than $PM_{2.5}$ for inducing inflammation [10]. UFPs have high cytotoxic reactive oxygen species (ROS) activity, through which numerous inflammatory responses are induced, compared to other particles [10]. Chronically elevated UFP levels such as those to which residents living near heavily trafficked roadways are likely exposed can lead to long-term or repeated increases in systemic inflammation that promote arteriosclerosis [18,29,34,37].

Asthma and highway exposures

Evidence that near highway exposures present elevated risk is relatively well developed with respect to child asthma studies. These studies have evolved over time with the use of different methodologies. Studies that used larger geographic frames and/or overall traffic in the vicinity of the home or school [49-52] or that used self-report of traffic intensity [53] found no association with asthma prevalence. Most recent child asthma studies have,

GL14 Continued

instead, used increasingly narrow definitions of proximity to traffic, including air monitoring or modeling) and have focused on major highways instead of street traffic [54-59]. All of these studies have found statistically significant associations between the prevalence of asthma or wheezing and living very close to high volume vehicle roadways. Confounders considered included housing conditions (pests, pets, gas stoves, water damage), exposure to tobacco smoke, various measures of socioeconomic status (SES), age, sex, and atopy, albeit self-reported and not all in a single study.

Multiple studies have found girls to be at greater risk than boys for asthma resulting from highway exposure [55,57,60]. A recent study also reports elevated risk only for children who moved next to the highway before they were 2 years of age, suggesting that early childhood exposure may be key [57]. The combined evidence suggests that living within 100 meters of major highways is a risk factor, although smaller distances may also result in graded increases in risk. The neglect of wind direction and the absence of air monitoring from some studies are notable missing factors. Additionally, recent concerns have been raised that geocoding (attaching a physical location to addresses) could introduce bias due to inaccuracy in locations [61].

Studies that rely on general area monitoring of ambient pollution and assess regional pollution on a scale orders of magnitude greater than the near-roadway gradients have also found associations between traffic generated pollution (CO and NOx) and prevalence of asthma [62] or hospital admission for asthma [63]. Lweguga-Mukasa et al. [64] monitored air up and down wind of a major motor vehicle bridge complex in Buffalo, NY and found that UFP were higher downwind, dropping off with distance. Their statistical models did not, however, support an association of UFP with asthma. A study in the San Francisco Bay Area measured $PM_{2.5}$, BC and NO_x over several months next to schools and found both higher pollution levels downwind from highways and a linear association of BC with asthma in long-term residents [60].

Gauderman et al. [65] measured NO_2 next to homes of 208 children. They found an odds ratio (OR) of 1.83 (confidence interval (CI): 1.04–3.22) for outdoor NO_2 (probably a surrogate for total highway pollution) and lifetime diagnosis of asthma. They also found a similar association with distance from residence to freeway. Self-report was used to control for numerous confounders, including tobacco smoke, SES, gas stoves, mildew, water damage, cockroaches and pets which did not substantially affect the association. Gauderman's study suggests that ambient air monitoring at the residence substantially increases statistical power to detect association of asthma with highway exposures.

Modeling of elemental carbon attributable to traffic near roadways based on ambient air monitoring of $PM_{2.5}$ has recently emerged as a viable approach and a study using this method found an association with infant wheezing. The modeled values appear to be better predictors than proximity. Elevation of the residence relative to traffic was also an important factor in this study [66]. A 2007 paper reported on modeled NO_2, $PM_{2.5}$ and soot and the association of these values with asthma and various respiratory symptoms in the Netherlands [67]. While finding modest statistically significant associations for asthma and symptoms, it is somewhat surprising that they found stronger associations for development of sensitization to food allergens.

Pediatric lung function and traffic-related air pollution

Studies of association of children's lung function with traffic pollutants have used a variety of measures of exposure, including: traffic density, distance to roadways, area (city) monitors, monitoring at the home or school and personal monitoring. Studies have assessed both chronic effects on lung development and acute effects and have been both cross-sectional and longitudinal. The wide range of approaches somewhat complicates evaluation of the literature.

Traffic density in school districts in Munich was associated with decreases in forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV1/FVC and other measures, although the 2-kilometer (km) areas, the use of sitting position for spirometry and problems with translation for non-German children were limitations [68]. Brunekreef et al. [69] used distance from major roadways, considered wind direction and measured black smoke and NO2 inside schools. They found the largest decrements in lung function in girls living within 300 m of the roadways.

A longitudinal study of children (average age at start = 10 years) in Southern California reported results at 4 [70] and 8 years [71]. Multiple air pollutants were measured at sites in 12 communities. Due to substantial attrition, only 42% of children enrolled at the start were available for the 8-year follow-up. Substantially lower growth in FEV_1 was associated with PM_{10}, NO_2, $PM_{2.5}$, acid vapor and elemental carbon at 4 and at 8 years. The analysis could not indicate whether the effects seen were reversible or not [72]. In 2007, it was reported from this same cohort that living within 500 m of a freeway was reported to be associated with reduced lung function [73].

GL14 Continued

A Dutch study [74] measured $PM_{2.5}$, NO_2, benzene and EC for one year at 24 schools located within 400 m of major roadways. While associations were seen between symptoms and truck traffic and measured pollutants, there was no significant association between any of the environmental measures and FVC < 85% or FEV_1 < 85%. Restricting the analysis to children living within 500 m of highways generally increased ORs.

Personal exposure monitoring of NO_2 as a surrogate for total traffic pollutants with 298 Korean college students found statistically significant associations with FEV_1, FEV_1/FVC, and forced expiratory volume between 25 and 75% (FEV_{25-75}), but not with FVC. The multivariate regression model presented suggests that FEV_{25-75} was the outcome measure that most clearly showed an effect [75]. Cross-sectional studies of children in Korea [76] and France [77] also indicate that lung function is diminished in association with area pollutants that largely derive from traffic.

Time series studies suggest there are also acute effects. A study of 19 asthmatic children measured PM via personally carried monitors, at homes and at central site monitors. The study found deficits in FEV_1 that were associated with PM, although many sources besides traffic contributed to exposure. In addition, the results suggest that ability to see associations with health outcomes improves at finer scale of monitoring [78]. PM was associated with reduced FEV_1 and FVC in only the asthmatic subset of children in a Seattle study [79]. Studies have also seen associations between PM and self reported peak flow measurements [80,81] and asthmatic symptoms [82].

Cancer and near highway exposures

As noted above, both the Six-Cities Study [27] and the American Cancer Society (ACS) Study [28] found associations between PM and lung cancer. Follow-up studies using the ACS cohort [29,37] and the Six-Studies cohort [83] that controlled for smoking and other risk factors also demonstrated significant associations between PM and lung cancer. The original studies were subject to intensive replication, validation, and re-analysis which confirmed the original findings [84].

The ASHMOG study [85] was designed to look specifically at lung cancer and air pollution among Seventh-day Adventists in California, taking advantage of their low smoking rates. Air pollution was interpolated to centroids of zip codes from ambient air monitoring stations. Highway proximity was not considered. The study found associations with ozone (its primary pollutant of consideration), PM10 and SO2. Notably, these are not the pollutants that would be expected to be substantially elevated immediately adjacent to highways.

A case control study of residents of Stockholm, Sweden modeled traffic-related NO2 levels at their homes over 30 years and found that the strongest association involved a 20 year latency period [86]. Another case control study drawn from the European Prospective Investigation on Cancer and Nutrition found statistically significantly elevated ORs for lung cancer with proximity to heavy traffic (>10,000 cars per day) as well as for NO_2 and PM_{10} at nearby ambient monitoring stations [87]. Nafstad et al. [88] used modeled NO_2 and SO_2 concentrations at the homes of over 16,000 men in Oslo to test associations with lung cancer incidence. The models included traffic and point sources. The study found small, but statistically significant associations between NO_2 and lung cancer. Problems that run through all these studies are weak measures of exposure to secondhand tobacco smoke, the use of main roads rather than highways as the exposure group and modeled rather than measured air pollutants.

A study of regional pollution in Japan and a case control study of more localized pollution in a town in Italy also found associations between NO_2 and lung cancer and PM and lung cancer [89,90]. On the other hand, a study that calculated SIRs for specific cancers across lower and higher traffic intensity found little evidence of an association with a range of cancers [91].

The plausibility of near-highway pollution causing lung cancer is bolstered by the presence of known carcinogens in diesel PM. The US EPA has concluded after reviewing the literature that diesel exhaust is "likely to be carcinogenic to humans by inhalation" [92]. An interesting study of UFP and DNA damage adds credibility to an association with cancer [93]. This study had participants bicycle in traffic in Copenhagen and measured personal exposure to UFP and DNA oxidation and strand breaks in mononuclear blood cells. Bicycling in traffic increased UFP exposure and oxidative damage to DNA, thus demonstrating an association between DNA damage and UFP exposure *in vivo*.

Policy and research recommendations

Based on the literature reviewed above it is plausible that gradients of pollutants next to highways carry elevated health risks that may be larger than the risks of general area ambient pollutants. While the evidence is considerable, it is not overwhelming and is weak in some areas. The strongest evidence comes from studies of development of asthma and reduction of lung function during childhood, while the studies of cardiac health risk require extrapolation from area studies of smaller and larger geographic scales and inference from toxicology laboratory investigations. The lung cancer studies, because they include pollutants such as O_3 that are not locally concentrated, are not particularly strong in terms of the case for near-high-

GL14 Continued

way risk. There is a need for lung cancer research that uses major highways rather than heavily trafficked roads as the environmental exposure.

While more studies of asthma and lung function in children are needed to confirm existing findings, especially studies that integrate exposure at school, home and during commuting, to refine our knowledge about the association, we would point to the greater need for studies of cardiac health and lung cancer and their association with near highway exposures as the primary research areas needing to be developed. Many of the studies of PM and cardiac or pulmonary health have focused on mortality. Near highway mortality studies may be possible, but would be lengthy if they were initiated as prospective cohorts. Other possibilities include retrospective case control studies of mortality, cross sectional studies or prospective studies that have end points short of mortality, such as biological markers of disease. For all health end points there is a need for studies that adequately address the possible confounding of SES with proximity to highways. There is good reason to think that property values decline near highways and that control for SES by, for example, income, may be inadequate.

Because of the incomplete development of the science regarding the health risks of near highway exposures and the high cost and implication of at least some possible changes in planning and development, policy decisions are complicated. The State of California has largely prohibited siting of schools within 500 feet of freeways (SB 352; approved by the governor October 2, 2003). Perhaps this is a viable model for other states or for national-level response. As it is the only such law of which we are aware, there may be other approaches that will be and should be tried. One limitation of the California approach is that it does nothing to address the population already exposed at schools currently cited near freeways and does not address residence near freeways.

Conclusion

The most susceptible (and overlooked) population in the US subject to serious health effects from air pollution may be those who live very near major regional transportation route, especially highways. Policies that have been technology based and regional in orientation do not efficiently address the very large exposure and health gradients suffered by these populations. This is problematic because even regions that EPA has deemed to be in regional PM "attainment" still include very large numbers of near highway residents who currently are not protected. There is a need for more research, but also a need to begin to explore policy options that would protect the exposed population.

Abbreviations

UFP = ultra fine particles

BC = black carbon

NO_2 = nitrogen dioxide

NOx = oxides of nitrogen

CO = carbon monoxide

PM = particulate matter

$PM_{2.5}$ = particulate matter less than 2.5 um

PM_{10} = particulate matter less than 10 um

PPAH = particle bound polyaromatic hydrocarbons

EC = elemental carbon

VOC = volatile organic compounds

SO_2 = sulfur dioxide

ACS = American Cancer Society

SES = socioeconomic status

EPA = Environmental Protection Agency

OR = odds ratio

FEV_1 = forced expiratory volume in 1 second

FEV_1/FVC = ratio of FEV_1 and forced vital capacity

FEV_{25-75} = forced expiratory volume between 25 and 75

FVC = forced vital capacity

ug/m^3 = micrograms per cubic meter of air

m = meters

um = micrometers

veh/d = vehicles per day

veh/h = vehicles per hour

Competing interests

The author{s} declare that they have no competing interests.

GL14 Continued

Authors' contributions

DB took the lead on the manuscript. He co-wrote the background and wrote the sections on asthma, lung function and cancer and the conclusions. JLD wrote the section on air pollutants near roadways and contributed substantially to the background. CR wrote the section on cardiovascular health. All authors participated in editing and refining the manuscript and all read it multiple times, including the final version.

Acknowledgements

We thank Wig Zamore for useful insights into the topic. The Jonathan M Tisch College of Citizenship and Public Service partially supported the effort of Doug Brugge and Christine Rioux. Figure 1 was reproduced with permission of the publisher.

References

1. **American Housing Survey for the United States: 2003 Series H150/03** [http://www.census.gov/hhes/www/housing/ahs/ahs03/ahs03.html]. Accessed May 2007.
2. Massachusetts Fact Book. 2004.
3. Chambers LA: **Classification and extent of air pollution problems.** In *Air Pollution Volume I*. 3rd edition. Edited by: Stern AC. Academic Press, NY; 1976.
4. Rogge WF, Hildemann LM, Mazurek MA, Cass GR, Simoneit BRT: **Sources of fine organic aerosol. 2. Noncatalyst and catalyst-equipped automobiles and heavy-duty diesel trucks.** *Environmental Science Technology* 1993, **27**:636-651.
5. Graedel TE, Hawkins DT, Claxton LD: **Atmospheric Chemical Compounds: Sources, Occurrence, and Bioassay.** Academic Press, Inc., New York, NY; 1986.
6. Shi JP, Khan AA, Harrison RM: **Measurements of ultrafine particle concentration and size distribution in the urban atmosphere.** *The Science of the Total Environment* 1999, **235**:51-64.
7. Zhu Y, Hinds WC, Kim S, Sioutas C: **Concentration and size distribution of ultrafine particles near a major highway.** *Journal of the Air and Waste Management Association* 2002, **52(9)**:1032-1042.
8. Zhu Y, Hinds WC, Kim S, Shen S, Sioutas C: **Study of ultrafine particles near a major highway with heavy-duty diesel traffic.** *Atmospheric Environment* 2002, **36**:4323-4335.
9. Zhang KM, Wexler AS, Zhu Y, Hinds WC, Sioutas C: **Evolution of particle number distribution near roadways. Part II: the 'Road-to-Ambient' process.** *Atmospheric Environment* 2004, **38**:6655-6665.
10. Sioutas C, Delfino RJ, Singh M: **Exposure assessment for atmospheric ultrafine particles (UFP) and implications in epidemiologic research.** *Environmental Health Perspectives* 2005, **113(8)**:947-955.
11. Hitchins J, Morawska L, Wolff R, Gilbert D: **Concentrations of submicrometre particles from vehicle emissions near a major road.** *Atmospheric Environment* 2000, **34**:51-59.
12. Morawska L, Thomas S, Gilbert D, Greenaway C, Rijnders E: **A study of the horizontal and vertical profile of submicrometer particulates in relation to a busy road.** *Atmospheric Environment* 1999, **33**:1261-1274.
13. Fischer PH, Hoek G, van Reeuwijk H, Briggs DJ, Lebret E, van Wijnen JH, Kingham S, Elliott PE: **Traffic-related differences in outdoor and indoor concentrations of particles and volatile organic compounds in Amsterdam.** *Atmospheric Environment* 2000, **34**:3713-3722.
14. Roorda-Knape MC, Janssen NAH, De Hartog JJ, van Vliet PHN, Harssema H, Brunekreef B: **Air pollution from traffic in city districts near major motorways.** *Atmospheric Environment* 1998, **32**:1921-1930.
15. Janssen NAH, van Vliet PHN, Aarts F, Harssema H, Brunekreef B: **Assessment of exposure to traffic related air pollution of children attending schools near motorways.** *Atmospheric Environment* 2001, **35**:3875-3884.
16. National Research Council, Committee on Research Priorities for Airborne Particulate Matter: **Research priorities for airborne particulate matter, IV: continuing research progress.** National Academy Press, Washington, DC; 2004.
17. US Environmental Protection Agency: *Air quality criteria for particulate matter* Research Triangle Park; 2004.
18. Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, Kaufman JD: **Long-term exposure to air pollution and incidence of cardiovascular events in women.** *The New England Journal of Medicine* 2007, **356**:447-458.
19. Riediker M, Cascio WE, Griggs TR, Herbst MC, Bromberg PA, Neas L, Williams RW, Devlin RB: **Particulate matter exposure in cars is associated with cardiovascular effects in healthy young men.** *American Journal of Respiratory and Critical Care Medicine* 2004, **169**:934-940.
20. Hoffmann B, Moebus S, Stang A, Beck E, Dragano N, Möhlenkamp S, Schmermund A, Memmesheimer M, Mann K, Erbel R, Jockel KH, Heinz Nixdorf RECALL Study Investigative Group: **Residence close to high traffic and prevalence of coronary heart disease.** *European Heart Journal* 2006, **27**:2696-2702.
21. Ruckerl R, Greven S, Ljungman P, Aalto P, Antoniades C, Bellander T, Berglind N, Chrysohoou C, Forastiere F, Jacquemin B, von Klot S, Koenig W, Kuchenhoff H, Lanki T, Peltonen J, Peruzzi CA, Schneider A, Suntyer J, Peters A: **Air pollution and inflammation (IL-6, CRP, fibrinogen) in myocardial infarction survivors.** *Environmental Health Perspectives* 2007, **115**:1072-1080.
22. Schwartz J, Litonjua A, Suh H, Verrier M, Zanobetti A, Syring M, Nearing B, Verrier R, Stone P, MacCallum G, Speizer FE, Gold DR: **Traffic related pollution and heart rate variability in a panel of elderly subjects.** *Thorax* 2005, **60**:455-461.
23. Adar SD, Gold DR, Coull BA, Schwartz J, Stone P, Suh H: **Focused exposures to airborne traffic particles and heart rate variability in the elderly.** *Epidemiology* 2007, **18**:95-103.
24. Hoek G, Brunekreek B, Goldbohm S, Fischer P, van den Brandt PA: **Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study.** *The Lancet* 2002, **360**:1203-1209.
25. Peters A, von Klot S, Heier M, Trentinaglia I, Hormann A, Wichmann HE, Lowel H: **Exposure to traffic and the onset of myocardial infarction.** *The New England Journal of Medicine* 2004, **351**:1861-70.
26. Pope CA, Dockery DW: **Health effects of fine particulate air pollution: lines that connect.** *Journal of Air and Waste Management* 2006, **56(6)**:709-742.
27. Dockery DW, Pope CA, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG, Speizer FE: **An association between air pollution and mortality in six U.S. cities.** *New England Journal of Medicine* 1993, **329**:1753-9.
28. Pope CA, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, Heth CW: **Particulate air pollution as a predictor of mortality in a prospective study of US adults.** *American Journal of Respiratory and Critical Care Medicine* 1995, **151**:669-674.
29. Pope CA, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, Thurston GD: **Lung Cancer, Cardiopulmonary mortality, and long-term exposure to fine particulate air pollution.** *Journal of the American Medical Association* 2002, **287**:1132-1141.
30. Kunzli N, Jerrett M, Mack WJ, Beckerman B, LaBree L, Gilliland F, Thomas D, Peters J, Hodis HN: **Ambient air pollution and Atherosclerosis in Los Angeles.** *Environmental Health Perspectives* 2005, **113**:201-206.
31. Peters A: **Particulate matter and heart disease: Evidence from epidemiological studies.** *Toxicology and Applied Pharmacology* 2005:477-482.
32. Wheeler A, Zanobetti A, Gold DR, Schwartz J, Stone P, Suh H: **The relationship between ambient air pollution and heart rate variability differs for individuals with heart and pulmonary disease.** *Environmental Health Perspectives* 2006, **114**:560-566.
33. Chuang K, Chan C, Chen N, Su T, Lin L: **Effects of particle size fractions on reducing heart rate variability in cardiac and hypertensive patients.** *Environmental Health Perspectives* 2005, **113**:1693-1697.
34. Chan C, Chuang K, Shiao G, Lin L: **Personal exposure to submicrometer particles and heart rate variability in human subjects.** *Environmental Health Perspectives* 2004, **112**:1063-1067.
35. Brauer M, Hoek G, van Vliet P, Meliefste K, Fischer P, Gehring U, Heinrich J, Cyrys J, Bellander T, Lewne M, Brunekreef B: **Estimating long-term average particulate air pollution concentrations: application of traffic indicators and geographic information systems.** *Epidemiology* 2003, **14**:228-239.

GL14 Continued

36. Brunekreef B, Holgate ST: **Air pollution and health.** *Lancet* 2002, **360**:1233-1242.
37. Jerrett M, Finkelstein M: **Geographies of risk in studies linking chronic air pollution exposure to health outcomes.** *Journal of Toxicology and Environmental Health* 2005, **68**:1207-1242.
38. O'Neill MS, Jerrett M, Kawachi I, Levy JI, Cohen AJ, Gouveia N, Wilkinson P, Fletcher T, Cifuentes L, Schwartz J: **Workshop on Air Pollution and Socioeconomic Conditions, Health, wealth, and air pollution: advancing theory and methods.** *Environmental Health Perspectives* 2003, **111**:1861-1870.
39. Jerrett M, Burnett RT, Ma R, Pope CA, Krewski D, Newbold KB, Thurston G, Shi Y, Finkelstein N, Calle EE, Thun MJ: **Spatial Analysis of Air Pollution and Mortality in Los Angeles.** *Epidemiology* 2005, **16(6)**:727-736.
40. Finkelstein M, Jerrett M, Sears MR: **Environmental inequality and circulatory disease mortality gradients.** *Journal of Epidemiology and Community Health* 2005, **59**:481-487.
41. Tonne C, Melly S, Mittleman M, Coull B, Goldberg R, Schwartz J: **A case-control analysis of exposure to traffic and acute myocardial infarction.** *Environmental Health Perspectives* 2007, **115**:53-57.
42. Lipfert FW, Wyzga RE, Baty JD, Miller JP: **Traffic density as a surrogate measure of environmental exposures in studies of air pollution health effects: Long-term mortality in a cohort of US veterans.** *Atmospheric Environment* 2006, **40**:154-169.
43. Pope CA, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ: **Cardiovascular mortality and long-term exposure to particulate air pollution – Epidemiological evidence of general pathophysiological pathways of disease.** *Circulation* 2004, **109**:71-77.
44. Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, Luepker R, Mittleman M, Samet J, Smith SC, Tager I: **Air pollution and cardiovascular disease: a statement for healthcare professionals from the expert panel on population and prevention science of the American Heart Association.** *Circulation* 2004, **109**:2655-2671.
45. Sun Q, Wang A, Jin X, Natanzon A, Duquaine D, Brook RD, Aguinaldo JG, Fayad Z, Fuster V, Lippman M, Chen LC, Rajagopalan S: **Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model.** *Journal of the American Medical Association* 2005, **294**:3003-3010.
46. Sanchis RS, Petroni DH, George WJ: **Ambient particulate matter, C-reactive protein, and coronary artery disease.** *Inhalation Toxicology* 2005, **17**:409-413.
47. Oberdorster G: **Pulmonary effects of inhaled ultrafine particles.** *International Archives of Occupational and Environmental Health* 2001, **65**:1531-1543.
48. Delfino RJ, Sioutas C, Malik S: **Potential role of ultrafine particles in associations between airborne particle mass and cardiovascular health.** *Environmental Health Perspectives* 2005, **113**:934-946.
49. Venn A, Lewis S, Cooper M, Hubbard R, Hill I, Boddy R, Bell M, Britton J: **Local road traffic activity and the prevalence, severity, and persistence of wheeze in school children: combined cross sectional and longitudinal study.** *Occupational & Environmental Medicine* 2000, **57**:152-158.
50. Waldron G, Puccia B, Dod J: **Asthma and the motorways – One district's experience.** *Journal of Public Health Medicine* 1995, **17**:85-89.
51. Lewis SA, Antoniak M, Venn AJ, et al: **Secondhand smoke, dietary fruit intake, road traffic exposures, and the prevalence of asthma: A cross-sectional study in young children.** *American Journal of Epidemiology* 2005, **161**:406-411.
52. English P, Neutra R, Scalf R, Sullivan M, Waller L, Zhu L: **Examining associations between childhood asthma and traffic flow using a geographic information system.** *Environmental Health Perspectives* 1999, **107**:761-767.
53. Heinrick J, Topp R, Gerwig U, Thefeld W: **Traffic at residential address, respiratory health, and atopy in adults; the National German Health Survey 1998.** *Environmental Research* 2005, **98**:240-249.
54. Van Vliet P, Knape M, de Hartog J, Janssen N, Harssema H, Brunekreef B: **Motor vehicle exhaust and chronic respiratory symptoms in children living near freeways.** *Environmental Research* 1997, **74**:122-132.
55. Venn AJ, Lewis SA, Cooper M, Hubbard R, Britton J: **Living near a main road and the risk of wheezing illness in children.** *American Journal of Respiratory and Critical Care Medicine* 2001, **164(12)**:2177-2180.
56. Venn A, Yemaneberhan H, Lewis S, Parry E, Britton J: **Proximity of the home to roads and the risk of wheeze in an Ethiopian population.** *Occupational and Environmental Medicine* 2005, **62**:376-380.
57. McConnell R, Berhane K, Yao L, Jerrett M, Lurmann F, Gilliland F, Kunzli N, Gauderman J, Avol E, Thomas D, Peters J: **Traffic susceptibility, and childhood asthma.** *Environmental Health Perspectives* 2006, **114**:766-772.
58. Nicolai T, Carr D, Weiland SK, Duhme H, von Ehrenstein O, Wagner C, von Mutius E: **Urban traffic and pollutant exposure related to respiratory outcomes and atopy in a large sample of children.** *European Respiratory Journal* 2003, **21**:956-963.
59. Ryan PH, LeMasters , Biswas P, Levin L, Hu S, Lindsey M, Bernstein DI, Lockey J, Villareal M, Hershey GKH, Grinshpun SA: **A comparison of proximity and land use regression traffic exposure models and wheezing in infants.** *Environmental Health Perspectives* 2007, **115**:278-284.
60. Kim JJ, Smorodinsky S, Lipsett M, Singer BC, Hodgson AT, Ostro B: **Traffic-related air pollution near busy roads: The East Bay children's respiratory health study.** *American Journal of Respiratory and Critical Care Medicine* 2004, **170**:520-526.
61. Ong P, Graham M, Houston D: **Policy and programmatic importance of spatial alignment of data sources.** *Am J Public Health* 2006, **96**:499-504.
62. Hwang BF, Lee YL, Lin YC, Jaakkola JJ, Guo YL: **Traffic related air pollution as a determinant of asthma among Taiwanese school children.** *Thorax* 2005, **60**:467-473.
63. Migliaretti G, Cadum E, Migliore E, et al: **Traffic air pollution and hospital admissions for asthma: A case control approach in a Turin (Italy) population.** *International Archives of Occupational and Environmental Health* 2005, **78**:164-169.
64. Lwebuga-Mukasa JS, Oyana TJ, Johnson C: **Local ecological factors, ultrafine particulate concentrations, and asthma prevalence rates in Buffalo, New York, neighborhoods.** *Journal of Asthma* 2005, **42**:337-348.
65. Gauderman WJ, Avol E, Lurmann F, Kuenzli N, Gilliland F, Peters J, McConnell R: **Childhood asthma and exposure to traffic and nitrogen dioxide.** *Epidemiology* 2005, **16**:737-743.
66. Ryan PH, LeMasters GK, Biswas P, Levin L, Hu S, Lindsey M: **A comparison of proximity and land use regression traffic exposure models and wheezing in infants.** *Environmental Health Perspectives* 2007, **115**:278-284.
67. Brauer M, Hoek G, Smit HA, de Jongste JC, Gerritsen J, Postma DS, Kerkhof M, Brunekreef B: **Air pollution and development of asthma, allergy and infections in a birth cohort.** *European Respiratory Journal* 2007, **29**:879-888.
68. Wjst M, Reitmeir P, Dodd S, Wolff A, Nicolai T, von Loeffelholz-Colberg EF, von Mutius E: **Road traffic and adverse effects on respiratory health in children.** *British Medical Journal* 1993, **307**:596-307.
69. Brunekreef B, Janssen NA, de Hartog J, Harssema H, Knape M, van Vliet P: **Air pollution from truck traffic and lung function in children living near motorways.** *Epidemiology* 1997, **8**:298-303.
70. Gauderman WJ, McConnell , Gilliland F, London S, Thomas D, Avol E, Vora H, Berhane K, Rappaport EB, Lurmann F, Margolis HG, Peters J: **Association between air pollution and lung function growth in Southern California Children.** *American Journal of Respiratory and Critical Care Medicine* 2000, **162(4 Pt 1)**:1383-1390.
71. Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, Berhane K, McConnell R, Kuenzli N, Lurmann F, Rappaport E, Margolis H, Bates D, Peters J: **The Effect of Air Pollution on Lung Development from 10 to 18 Years of Age.** *New England Journal of Medicine* 2005, **351**:1057-67.
72. Markus PJFM: **Air pollution and lung function.** *New England Journal of Medicine* 2005, **351**:2652.
73. Gauderman WJ, Vora H, McConnell R, Berhane K, Gilliland F, Thomas D, Lurmann F, Avol E, Kunzli N, Jerrett M, Peters J: **Effect of exposure to traffic on lung development from 10 to 18 years of age: A cohort study.** *The Lancet* 2007, **369**:571-577.
74. Janssen NA-H, Brunekreef B, van Vliet P, Aarts F, Meliefste K, Harssema H, Fischer P: **The relationship between air pollution from heavy traffic and allergic sensitization, bronchial hyperresponsiveness, and respiratory symptoms in Dutch school children.** *Environmental Health Perspectives* 2003, **111**:1512-1518.
75. Hong Y-C, Leem J-H, Lee K-H, Park D-H, Jang J-Y, Kim S-T, Ha E-H: **Exposure to air pollution and pulmonary function in university students.** *International Archives of Occupational and Environmental Health* 2005, **78**:132-138.
76. Kim HB, Lim DH, Kim JK, Jeong SJ, Son BK: **Effects of particulate matter (PM10) on pulmonary function of middle school children.** *Journal of the Korean Medical Society* 2005, **20(1)**:42-45.
77. Penard-Morand C, Charpin D, Raherison C, Kopferschmitt C, Caillaud D, Lavaud F, Annesi-Maesano I: **Long-term exposure to background air pollution related to respiratory and allergic health in schoolchildren.** *Clinical and Experimental Allergy* 2005, **35**:1279-1287.
78. Delfino RJ, Quintana PJE, Floro J, Gastanaga VM, Samimi BS, Kleinman MT, Liu LJ, Bufalino C, Wu C, McLaren CE: **Association of FEV1 in asthmatic children with personal and microenvironment exposure to airborne particulate matter.** *Environmental Health Perspectives* 2004, **112**:932-941.
79. Koenig JQ, Larson TV, Hanley QS, Rebolledo V, Dumler K, Checkoway H, Wang SZ, Lin D, Pierson WE: **Pulmonary function changes in children associated with fine particulate matter.** *Environmental Research* 1993, **63**:26-38.
80. Van der Zee SC, Hoek G, Boezen HM, Schouten JP, van Wijnen JH, Brunekreef B: **Acute effects of urban air pollution on respiratory health of children with and without chronic respiratory symptoms.** *Occupational and Environmental Medicine* 1999, **56(12)**:802-813.
81. Pekkanen J, Timonen KL, Ruuskanen J, Reponen A, Mirme A: **Effects of ultrafine and fine particulates in urban air on peak expiratory flow among children with asthmatic symptoms.** *Environmental Research* 1997, **74**:24-33.
82. Peters JM, Avol E, Navidi W, London SJ, Gauderman WJ, Lurmann F, Linn WS, Margolis H, Rappaport E, Gong H, Thomas DC: **A study of twelve Southern California communities with differing levels and types of air pollution: Prevalence of respiratory morbidity.** *American Journal of Respiratory and Critical Care Medicine* 1999, **159(3)**:760-767.
83. Laden F, Schwartz J, Speizer FE, Dockery DE: **Reduction in fine particulate air pollution and mortality: extended follow-up of the Harvard six-cities study.** *American Journal of Respiratory and Critical Care Medicine* 2006, **173**:667-672.
84. Health Effects Institute: **Reanalysis of the Harvard six cities study and the American Cancer Society study of particulate air pollution mortality.** *Final Version; Boston, MA* 2000.
85. Besson WL, Abbey DE, Knutsen SF: **Long-term concentrations of ambient air pollutants and incident lung cancer in California adults: Results from the ASHMOG study.** *Environmental Health Perspectives* 1998, **106**:813-823.
86. Nyberg F, Gustavsson P, Jarup L, Bellander T, Berglind N, Jakobsson R, Pershagen G: **Urban air pollution and lung cancer in Stockholm.** *Epidemiology* 2000, **11**:487-495.
87. Vineis P, Hoek G, Krzyzanowski M, Vigna-Tagliani F, Veglia F, Airoldi L, Autrup H, Dunning A, Garte S, Hainaut P, Malaveille C, Matullo G, Overvad K, Raaschou-Nielsen O, Clavel-Chapelon F, Linseisen J, Boeing H, Trichopoulou A, Palli D, Pelucio M, Krogh V, Tumino R, Panico S, Bueno-De-Mesquita HB, Peeters PH, Lund EE, Gonzalez CA, Martinez C, Dorronsoro M, Barricarte A, Cirera L, Quiros JR, Berglund G, Forsberg B, Day NE, Key TJ, Saracci R, Kaaks R, Riboli E: **Air pollution and risk of lung cancer in a prospective study in Europe.** *International Journal of Cancer* 2006, **119**:169-174.
88. Nafstad P, Haheim LL, Oftedal B, Gram F, Holme I, Hjermann I, Leren P: **Lung cancer and air pollution: A 27-year follow up of 16 209 Norwegian men.** *Thorax* 2003, **58**:1071-1076.
89. Choi K-S, Inoue S, Shimozaki K: **Air pollution, temperature, and regional differences in lung cancer mortality in Japan.** *Archives of Environmental Health* 1997, **52**:160.
90. Biggeri A, Barbone F, Lagazio C, Bovenzi M, Stanta G: **Air pollution and lung cancer in Trieste, Italy: Spatial analysis of risk as a function of distance from sources.** *Environmental Health Perspectives* 1996, **104**:750-754.
91. Visser O, van Wijnen JH, van Leeuwen FE: **Residential traffic density and cancer incidence in Amsterdam, 1989–1997.** *Cancer Causes & Control* 2004, **15**:331-339.
92. US Environmental Protection Agency: **Health Assessment Document for Diesel Engine Exhaust. Washington, DC.** 2002.
93. Vinzents PS, Moller P, Sorensen M, Knudsen LE, Hertel O, Jensen FP, et al.: **Personal exposure to ultrafine particulates and oxidative DNA damage.** *Environmental Health Perspectives* 2005, **113**:1485-1490.

GL14 Continued

GL14 Continued

Attachment H

Gauderman, James W. et al.
Effects of Exposure to Traffic on Lung Development from 10 to 18 Years of Age: A Cohort Study
Lancet, Vol. 368
2006

GL14 Continued

This page intentionally left blank.

GL14 Continued

Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study

W James Gauderman, Rita Vora, Rob McConnell, Kiros Berhane, Frank Gilliland, Duncan Thomas, Fred Lurmann, Edward Avol, Nino Kunzli, Michael Jerrett, John Peters

Summary

Background Whether local exposure to major roadways adversely affects lung-function growth during the period of rapid lung development that takes place between 10 and 18 years of age is unknown. This study investigated the association between residential exposure to traffic and 8-year lung-function growth.

Methods In this prospective study, 3677 children (mean age 10 years [SD 0·44]) participated from 12 southern California communities that represent a wide range in regional air quality. Children were followed up for 8 years, with yearly lung-function measurements recorded. For each child, we identified several indicators of residential exposure to traffic from large roads. Regression analysis was used to establish whether 8-year growth in lung function was associated with local traffic exposure, and whether local traffic effects were independent of regional air quality.

Findings Children who lived within 500 m of a freeway (motorway) had substantial deficits in 8-year growth of forced expiratory volume in 1 s (FEV_1, −81 mL, p=0·01 [95% CI −143 to −18]) and maximum midexpiratory flow rate (MMEF, −127 mL/s, p=0·03 [−243 to −11]), compared with children who lived at least 1500 m from a freeway. Joint models showed that both local exposure to freeways and regional air pollution had detrimental, and independent, effects on lung-function growth. Pronounced deficits in attained lung function at age 18 years were recorded for those living within 500 m of a freeway, with mean percent-predicted 97·0% for FEV_1 (p=0·013, relative to >1500 m [95% CI 94·6–99·4]) and 93·4% for MMEF (p=0·006 [95% CI 89·1–97·7]).

Interpretation Local exposure to traffic on a freeway has adverse effects on children's lung development, which are independent of regional air quality, and which could result in important deficits in attained lung function in later life.

Lancet 2006; 368:

Department of Preventive Medicine, University of Southern California, 1540 Alcazar Street, Suite 220, Los Angeles, CA 90033, USA (WJ Gauderman PhD, H Vora MS, Prof R McConnell MD, K Berhane PhD, Prof F Gilliland MD, Prof D Thomas PhD, E Avol MS, Prof J Peters MD); Sonoma Technology Inc, #C, Petaluma, CA 94954, USA (F Lurmann MS); Respiratory and Environmental Research Unit, Institut Municipal d'Investigació Mèdica, C Doctor Aiguader, 80, 08003 Barcelona, Spain (N Kunzli MD); and Division of Environmental Health Sciences, School of Public Health, University of California, Berkeley, CA 94720-7360, USA (M Jerrett PhD)

Correspondence to: Dr W James Gauderman jimg@usc.edu

Introduction

Both cross-sectional[1–5] and longitudinal[6–8] studies have shown that lung function in children is adversely affected by exposure to urban, regional air pollution. Evidence has emerged that local exposure to traffic is related to adverse respiratory effects in children, including increased rates of asthma and other respiratory diseases.[9–11] Cross-sectional studies in Europe have shown that deficits in lung function are related to residential exposure to traffic.[12–14] However does traffic exposure have an adverse effect on lung-function development in children? The answer to this question is important in view of the extent of traffic exposure in urban environments and the established relation between diminished lung function in adulthood and morbidity and mortality.[15,16]

We investigated the association between residential exposure to traffic and 8-year lung-function development on the basis of cohort data from the Children's Health Study. We also studied the joint effects of local traffic exposure and regional air quality on children's lung development.

Methods

Participants

The Children's Health Study recruited two cohorts of fourth-grade children (mean age 10 years [SD 0·44], one in 1993 (cohort 1, n=1718) and the other in 1996 (cohort 2, n=1959). All children were recruited from schools in 12 southern California communities as part of an investigation into the long-term effects of air pollution on children's respiratory health.[7,8,17] A consistent protocol was used in all communities to identify schools, and all students targeted for study were invited to participate.[17] Overall, 82% (3677) of available students agreed to participate. Pulmonary-function data were obtained yearly by trained field technicians, who travelled to study schools to undertake maximum effort spirometry on the children, using the same equipment and testing protocol used throughout the study period. Details of the testing protocol have been previously reported.[7,8] Children in both cohorts were followed up for 8 years.

A baseline questionnaire, completed at study entry by each child's parent or legal guardian, was used to obtain information on race, Hispanic ethnic origin, parental income and education, history of doctor-diagnosed asthma, in-utero exposure to maternal smoking, and household exposure to gas stoves, pets, and environmental tobacco smoke.[18] A yearly questionnaire, with similar structure to that of the baseline questionnaire, was used to update information on asthma status, personal smoking, and exposure to environmental tobacco smoke. For statistical modelling, a three-category socioeconomic status variable was created on the basis of total household income and education of the parent or guardian that completed the questionnaire. High socioeconomic status (23% of children, n=823) was defined as a parental

GL14 Continued

income greater than US$100 000 per year, or an income over US$15 000 per year and at least 4 years of college education. The middle category (36%, n=1283) included children with a parental income between US$15 000 and US$100 000 and some (less than 4 years) college or technical school education, and low socioeconomic status (41%, n=1483) included all remaining children.

The study protocol was approved by the institutional review board for human studies at the University of Southern California, and written consent was provided by a parent or legal guardian for every study participant.

Exposure Data

We characterised exposure of every study participant to traffic-related pollutants by two types of measures—proximity of the child's residence to the nearest freeway or to the nearest major non-freeway road, and model-based estimates of traffic-related air pollution at the residence, derived from dispersion models that incorporated distance to roadways, vehicle counts, vehicle emission rates, and meteorological conditions.[18] Regional air pollution was continuously monitored at one central site location within each study community over the course of the investigation. Further details of exposure assessment are available in the webappendix.

See Online for webappendix

Statistical methods

The outcome data consisted of 22 686 pulmonary-function tests recorded from 3677 participants during 8 years in both cohorts. We focused on three pulmonary-function measures: forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and maximum midexpiratory flow rate (MMEF, also known as FEF_{25-75}). The exposures of primary interest were the traffic measures described above.

We used a hierarchical mixed-effects model to relate 8-year growth in each lung-function measure to traffic exposure, with basic structure that has been previously described.[19] To account for the growth pattern in lung function during this period, we used a linear spline model,[20] constructed so that 8-year growth in lung function was estimated jointly with other model parameters. We estimated and tested the effect of traffic exposure on 8-year growth, and in some analyses on mean values at 10 and 18 years of age. The model allowed for separate growth curves for each sex, race, ethnic origin, cohort, and baseline-asthma subgroup. The model also included adjustments for height, height squared, body-mass index (BMI), BMI squared, present asthma status, exercise or respiratory illness on the day of the test, any tobacco smoking by the child in the previous year, and indicator variables for field technician. Random effects for the intercept and 8-year growth parameters were included at the level of participant and community.

To keep the potential effect of outliers to a minimum and to examine possible non-linear exposure-response relations, we used categorical forms of each traffic indicator in our models. For distance to the freeway, we formed four categories—less than 500 m, 500–1000 m, 1000–1500 m, and more than 1500 m. Distances to non-freeway major roads were similarly categorised based on distances of 75 m, 150 m, and 300 m. Model-based estimates of pollution from freeways and non-freeways were categorised into quartiles on the basis of their respective distributions (see webappendix). The categorisation distances for all traffic indicators were fixed before any health analyses were done. Traffic effects are reported as the difference in 8-year growth for each category relative to the least exposed category, so that negative estimates signify reduced lung-function growth or values with increased exposure.

We also considered joint estimation of traffic effects within the community and pollution between communities, which was based on the long-term average pollutant concentrations measured at the central sites (see webappendix). Pollutant effects are reported as the difference in 8-year growth in lung function from the least to the most polluted community, with negative differences indicating growth deficits with increased exposure. Possible modification of a traffic effect by community-average ambient pollutant concentration was tested by inclusion of the appropriate interaction term in the model.

To examine attained lung function, we computed percent-predicted lung function for participants who were measured in 12th grade, our last year of follow-up (n=1497, mean age 17·9 years, [SD=0·41]). To estimate predicted FEV_1 values, we first fitted a regression model for observed FEV_1 (log transformed) with predictors log height, BMI, BMI squared, sex, asthma status, race or ethnic origin, field technician, and sex-by-log height, sex-by-BMI, sex-by-BMI squared, sex-by-asthma, and sex-by-race or ethnic origin interactions. We calculated predicted FEV_1 on the basis of this model and percent-predicted as observed divided by predicted FEV_1. We used a regression model to calculate the mean percent-predicted value for each category of distance to the freeway, with adjustment for community. To aid in interpretation, we scaled percent-predicted values so that children who lived furthest (>1500 m) from a freeway had a mean of 100%, and we give means for the remaining distance groups relative to this benchmark. Analogous calculations were used to obtain the percent-predicted mean for FVC and MMEF.

Regression procedures in SAS (version 9·0) were used to fit all models. Associations denoted as significant were those with a p value less than 0·05, assuming a two-sided alternative hypothesis.

Role of the funding source

The funding sources of this study had no role in the study design, collection, analysis, or interpretation of data, in the writing of the report, or in the decision to submit the paper for publication. The corresponding

GL14 Continued

author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

An average of 6·2 pulmonary function tests were done per child. There were equal proportions of male and female participants (webtable 1). Most children were of non-Hispanic white or Hispanic ethnic origin. 440 (12%) children lived within 500 m of a freeway, with most of these children residing in six of the 12 communities (webtable 2 and webfigure). Model-based estimates of pollution from a freeway were skewed toward either high or low values within most study communities.

8-year growth in FVC, FEV_1, and MMEF averaged 1512 mL, 1316 mL, and 1402 mL/s, respectively, in girls, and 2808 ml, 2406 ml, and 2476 ml/s, respectively, in boys. Closer residential distance to a freeway was associated with reduced growth in lung function (table 1). In children who lived within 500 m of a freeway, 8-year growth was significantly reduced compared with those who lived at least 1500 m from a freeway. Large deficits in FEV_1 and MMEF growth were also estimated for the two highest-exposure quartiles of model-based pollution from a freeway, although neither deficit was statistically significant. Indicators of traffic from non-freeway roads, including both distance and model-based pollution estimates, were not associated with reduced growth.

The association between FEV_1 growth and distance to a freeway was significant in various sensitivity analyses (table 2). Compared with the results shown in table 1 (base model), distance-effect estimates were larger with additional adjustment for socio-economic status. Further investigation showed that low socioeconomic status was associated with increased traffic exposure, with mean residential distance to freeways of 1·8 km (SD 1·32), 2·0 km (1·65), and 2·5 km (1·91) for low, middle, and high groups respectively. However, socioeconomic status was not significantly associated with FEV_1 growth, and therefore adjustment for this variable induced only a modest change. Adjustment for indoor sources of air pollution including gas stoves, pets, and exposure to environmental tobacco smoke also resulted in little change in the estimated freeway-distance effects.

Significant distance effects were seen in the subset of children who reported never having had asthma, and in the subset of children who reported no active tobacco smoking. The relation between FEV_1 growth and distance was noticeably larger in boys than in girls, although a test of effect modification by sex was non-significant (p=0·10). Only six of the 12 communities had substantial numbers of children living within 500 m of a freeway. The estimated effects of freeway distance on lung development were more pronounced in these six higher-traffic communities than in the other communities. There was no significant evidence of heterogeneity in the local distance effects between these six communities (data not shown).

	FVC (mL) difference (95% CI)	FEV1 (mL) difference (95% CI)	MMEF (mL/sec) difference (95% CI)
Freeway distance*			
<500 m	−63 (−131 to 5)	−81 (−143 to −18)	−127 (−243 to −11)
500–1000 m	−31 (−93 to 32)	−41 (−99 to 17)	−35 (−142 to 73)
1000–1500 m	−19 (−84 to 46)	−33 (−93 to 26)	−94 (−204 to 15)
Model-based pollution from freeway†			
4th quartile (high)	−66 (−186 to 54)	−60 (−179 to 42)	−147 (−357 to 58)
3rd quartile	−61 (−151 to 29)	−78 (−161 to 5)	−144 (−298 to 9)
2nd quartile	−27 (−90 to 36)	−22 (−80 to 36)	−37 (−144 to 71)
Non-freeway distances‡			
<75 m	5 (−63 to 72)	−35 (−97 to 27)	−66 (−181 to 40)
75–150 m	4 (−59 to 68)	22 (−37 to 80)	35 (−74 to 144)
150–300 m	−10 (−63 to 42)	−8 (−56 to 40)	−16 (−105 to 73)
Model-based pollution from non-freeway†			
4th quartile (high)	13 (−70 to 96)	3 (−74 to 80)	2 (−140 to 144)
3rd quartile	42 (−27 to 111)	16 (−47 to 80)	−23 (−141 to 95)
2nd quartile	6 (−54 to 66)	2 (−53 to 57)	11 (−91 to 113)

*Difference in 8-year lung-function growth relative to children living at least 1500 m from a freeway. †Difference in 8-year lung-function growth relative to children in the first (lowest) quartile of exposure. ‡Difference in 8-year lung-function growth relative to children living at least 300 m from a non-freeway road.

Table 1: Association between 8-year lung-function growth and several indicators of residential traffic exposure

	Freeway Distance (m)					
	<500	p	500–1000	p	1000–1500	p
Base model*	−81	0·012	−41	0·165	−33	0·275
Additional covariates						
Base+socioeconomic status	−92	0·005	−50	0·097	−37	0·228
Base+gas stove in the home	−85	0·008	−42	0·160	−33	0·281
Base+pets in the home	−80	0·013	−41	0·165	−33	0·275
Base+in-utero exposure to maternal smoking	−83	0·011	−33	0·266	−36	0·245
Base+second-hand smoke exposure	−85	0·008	−41	0·163	−37	0·230
Subgroups						
Non-asthmatics only	−83	0·025	−70	0·047	−61	0·094
Non-smokers only	−93	0·006	−45	0·154	−45	0·182
Boys only	−158	0·003	−54	0·264	−77	0·123
Girls only	−12	0·750	−39	0·254	3	0·932
Six communities with closest freeway proximity†	−105	0·003	−56	0·101	−40	0·260
Deleting observations after a residence change‡	−86	0·030	−73	0·042	−53	0·148

*Base model results are the same as those in table 1. All models include adjustment for the covariates listed in the Methods section. Values are the difference in 8-year FEV_1 growth relative to those living >1500 m from a freeway. †Including only children from the six communities with the largest number of children living near a freeway (Riverside, Atascadero, Alpine, San Dimas, Long Beach, and Santa Maria). ‡Censoring any pulmonary function tests recorded after a participant left his or her baseline address.

Table 2: Sensitivity analysis of freeway-distance effects on 8-year FEV_1 growth

Furthermore, around 34% (1257) of children moved from their baseline residence during follow-up but remained in one of the 12 study communities and thus continued to participate. If we omitted post-move lung-function measurements from the analysis, the estimated effects of freeway-distance on FEV_1 growth were more pronounced.

See Online for webtables 1 and 2 and webfigure

GL14 Continued

	Regional pollutant effect*	p	Local freeway distance (m)						
			<500	p	500–1000	p	1000–1500	p	p for interaction†
1000–1800 ozone	−13	0·821	−81	0·012	−41	0·165	−33	0·275	0·51
Nitrogen dioxide	−109	0·003	−80	0·012	−41	0·166	−33	0·279	0·81
Acid	−111	0·002	−80	0·013	−41	0·164	−33	0·285	0·54
PM_{10}	−111	0·013	−81	0·012	−42	0·158	−32	0·287	0·24
$PM_{2.5}$	−110	0·009	−80	0·012	−41	0·160	−33	0·285	0·40
Elemental carbon	−101	0·001	−80	0·012	−42	0·156	−33	0·282	0·63

*Pollutant effects are the difference in 8-year FEV_1 growth from lowest to highest observed community-average concentration of the pollutant, specifically: per increase of 37·5 ppb ozone (1000–1800), 34·6 ppb of nitrogen dioxide, 9·6 ppb of acid vapour, 51·4 μg/m³ of PM10, 22·8 μg/m³ of PM2·5 and 1·2 μg/m³ elemental carbon. Distance effects are the difference in 8-year growth relative to those living >1500 m from a freeway. †A test of whether freeway-distance effect is modified by regional concentration of the pollutant. PM_{10}=particulate matter <10 μm aerodynamic diameter. $PM_{2.5}$=particulate matter <2·5 μm aerodynamic diameter.

Table 3: Joint effect of regional pollution and local distance to a freeway on 8-year FEV_1 growth

Reduced lung-function growth was independently associated with both freeway distance and with regional air pollution (table 3). Statistically significant joint models of regional pollution with distance to freeway were seen for nitrogen dioxide, acid vapour, elemental carbon, and particulate matter with aerodynamic diameter less than 10 μm and less than 2·5 μm. Ozone was not associated with reduced lung-function growth. There was no significant evidence of effect modification (interaction) of local traffic effects with any of the regional pollutants.

A subset of 1445 children were observed over the full 8 years of the study, from age 10 to 18 years. In this group, we noted significant deficits in 8-year FEV_1 growth and MMEF growth for those who lived within 500 m of a freeway (table 4). At 10 years of age, there was some evidence of reduced lung function for those who lived closer to a freeway than those who did not, although none of the differences between distance categories was statistically significant. However, by 18 years of age, participants who lived closest to a freeway had substantially lower attained FEV_1 and MMEF than those who lived at least 1500 m from a freeway.

These deficits in average FEV_1 and MMEF translated into pronounced deficits in percent-predicted lung function at 18 years of age (figure). There was a trend of lower percent-predicted lung function for children who lived closer to a freeway than for those who lived further away. The effect was most pronounced for those who lived less than 500 m from a freeway, with average percent predicted values of 97·0% (95% CI 94·6–99·4) for FEV_1 (p=0·013 relative to >1500 m) and 93·4% (89·1–97·7) for MMEF (p=0·006).

		Lung function		8-year growth
		Age 10 years	Age 18 years	Difference* (95% CI)
		Difference* (95% CI)	Difference* (95% CI)	
FVC	Freeway distance			
	<500 m	−17 (−70 to 37)	−85 (−192 to 22)	−69 (−160 to 22)
	500–1,000 m	−12 (−61 to 37)	−54 (−151 to 43)	−42 (−125 to 41)
	1000–1500 m	−10 (−80 to 71)	−81 (−181 to 19)	−52 (−137 to 33)
FEV_1	Freeway distance			
	<500 m	−23 (−73 to 28)	−121 (−219 to −23)	−98 (−182 to −15)
	500–1000 m	−32 (−78 to 14)	−93 (−183 to −4)	−61 (−137 to 15)
	1000–1500 m	−34 (−81 to 14)	−78 (−170 to 14)	−44 (−122 to 34)
MMEF	Freeway distance			
	<500 m	−57 (−169 to 56)	−230 (−432 to −28)	−173 (−327 to −19)
	500–1000 m	−92 (−195 to 10)	−105 (−289 to 79)	−12 (−152 to 128)
	1000–1500 m	−45 (−150 to 60)	−151 (−340 to 38)	−106 (−250 to 38)

*Difference in 8-year lung function or growth relative to children living >1500 m from a freeway.

Table 4: Cumulative effect of residential distance in the 1445 children with full 8-year of follow-up

Discussion

This study shows that residential proximity to freeway traffic is associated with substantial deficits in lung-function development in children. 8-year increases in both FEV_1 and MMEF were smaller for children who lived within 500 m of a freeway, than for those who lived at least 1500 m from a freeway. Freeway effects were seen in subsets of non-asthmatic and non-smoking participants, which is an indication that traffic exposure has adverse effects on otherwise healthy children. Deficits in 8-year growth resulted in lower attained FEV_1 and MMEF at 18 years of age for participants who lived within 500 m of a freeway than for those who lived further away. Since lung development is nearly complete by age 18 years, an individual with a deficit at this time will probably continue to have less than healthy lung function for the remainder of his or her life.

We previously reported an association between community-average pollutant concentrations and 8-year lung-function growth.[9] That result relied on comparisons in communities that had different concentrations of regional air pollution, and implicated many pollutants such as nitrogen dioxide, acid vapour, particulate matter with aerodynamic diameter less than 10 μm and 2·5 μm, and elemental carbon. Our present study builds on that result, and shows that in addition to regional pollution, local exposure to large roadways are associated with diminished lung-function

GL14 Continued

GL14 Continued

development in children. We did not find any evidence that traffic effects varied depending on background air quality, which suggests that even in an area with low regional pollution, children living near a major roadway are at increased risk of health effects. Our results also suggest that children who live close to a freeway in a high pollution area experience a combination of adverse developmental effects because of both local and regional pollution.

We noted a larger freeway effect in boys than in girls, although the difference between sexes was not significant. By contrast, a cross-sectional European study[27] reported larger traffic effects on lung function in girls than in boys.[29] Several factors could explain this discrepancy in sex-specific effects between studies, from differences in specific air pollution mixtures and underlying population susceptibilities, to the general difficulty of comparisons between longitudinal and cross-sectional study effect estimates. In general, however, both studies show that lung function in children is adversely affected by exposure to traffic.

The concentrations of several pollutants are raised near major freeways. Daytime concentrations of black carbon, ultrafine particulate, and other exhaust pollutants have been reported to be high, but decline exponentially, within 500 m of a freeway,[6–8] although night-time concentrations of ultrafine particulate remain above background concentrations for distances greater than 500 m from a freeway.[8] Some studies have reported increased traffic pollution, particularly nitrogen dioxide, at distances over 1000 m from a freeway.[18,45,47] Elemental carbon, an indicator of pollution from diesel exhaust, varies with nearby high-traffic roads[47,53,55] but can also be transported across large distances.[12] Diesel exhaust is one of the primary contributors to particulate-matter concentrations in those communities most affected by traffic.[51] A pollutant such as elemental carbon could explain our reported health effects both locally and regionally.

Both regional ambient and ultrafine particulate matter present in high concentration in close proximity to roadways can elicit oxidative and nitrosative stress in the airways, which results in inflammation.[54,55] Kulkarni and co-workers[32] reported that traffic-related particulate matter was correlated with the amount of carbon in the airway macrophages of children, which in turn was associated with reductions in FEV_1, MMEF, and FVC. Chronic airway inflammation could produce our reported deficits in increased MMEF and FEV_1. Additional research is needed to identify the specific traffic pollutants that bring about health effects, and to elucidate the contribution of each pollutant to regional and local associations.

A strength of this study was the long-term, prospective follow-up of two large cohorts of children, with exposure and outcome data obtained consistently. However, as in any epidemiological study, our results could be confounded by one or more other factors related to both traffic and lung-function growth. Our results were robust to adjustment for several factors, including socioeconomic status and indoor sources of air pollution, but the possibility of confounding by other factors still exists. Throughout the 8-year follow-up, we noted around an 11% loss of study participants per year. Participant attrition is a potential source of bias in cohort studies. We analysed the subset of children who were followed up for the full 8-year duration of the study and also noted significant traffic-effect estimates, which make participant loss an unlikely explanation for our results. We did not note a significant association between growth and model-based pollution from a freeway, despite large estimated deficits in the highest-exposure quartiles (table 1). However, we were restricted in detection of an association with model-based pollution from freeways because there was little variation in this measure within most of our study communities (webtable 2).

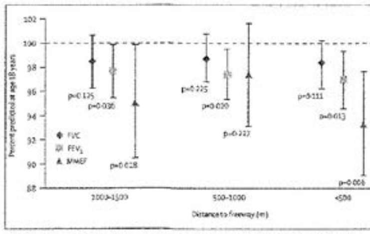


Figure: Percent-predicted lung function at age 18 years versus residential distance from a freeway
The horizontal line at 100% corresponds to the referent group, children living >1500 m from a freeway.

We have shown that residential distance from a freeway is associated with significant deficits in 8-year respiratory growth, which result in important deficits in lung function at age 18 years. This study adds to evidence that the present regulatory emphasis on regional air quality might need to be modified to include consideration of local variation in air pollution. In many urban areas, population growth is forcing the construction of housing tracts and schools near to busy roadways, with the result that many children live and attend school in close proximity to major sources of air pollution. In view of the magnitude of the reported effects and the importance of lung function as a determinant of adult morbidity and mortality, reduction of exposure to traffic-related air pollutants could lead to substantial public-health benefits.

Contributors

W J Gauderman, R McConnell, F Gilliland, E Avol, J Peters, M Jerrett and N Kunzli participated in the writing of the manuscript. W J Gauderman, H Vora, K Berhane, D Thomas, and F Lurmann participated in the analysis of the data. All named authors took part in the interpretation of results, and approved the final version of the manuscript.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

This study was supported in part by the California Air Resources Board (contract A033-186), the National Institute of Environmental Health Sciences (P01ES11627 and P30ES07048), and the Hastings Foundation. We thank Cheryl Fawcett for helpful discussions, members of our external advisory committee (Jonathan Samet, Nan Laird, Steve Rich, Petros Koutrakis, Gerhardt Coetzee) for important input, the school principals, teachers, students, and parents in each of the 12 study communities for their cooperation and the health testing field team.

References

1 Ware J, Ferris BJ, Dockery D, Spengler J, Stram D, Speizer F. Effects of ambient sulfur oxides and suspended particles on respiratory health of preadolescent children. *Am Rev Respir Dis* 1986; 133: 834–42.

2 Dockery D, Speizer F, Stram D, Ware J, Spengler J, Ferris BJ. Effects of inhalable particles on respiratory health of children. *Am Rev Respir Dis* 1989; 139: 587–94.

3 Schwartz J. Lung function and chronic exposure to air pollution: a cross-sectional analysis of NHANES II. *Environ Res* 1989; 50: 309–21.

4 Raizenne M, Neas L, Damokosh A, et al. Health effects of acid aerosols on North American children: pulmonary function. *Am Rev Respir Dis* 1993; 147: A635.

5 Bascom R, Bromberg P, Costa D, et al. State of the art: health effects of outdoor air pollution, part 1. *Am J Respir Crit Care Med* 1996; 153: 3–50.

6 Bascom R, Bromberg P, Costa D, et al. State of the art: health effects of outdoor air pollution, part 2. *Am J Respir Crit Care Med* 1996; 153: 477–98.

7 Peters J, Avol E, Gauderman W, et al. A study of twelve southern California communities with differing levels and types of air pollution II. Effects on pulmonary function. *Am J Respir Crit Care Med* 1999; 159: 768–75.

8 Kunzli N, Lurmann F, Segal M, Ngo L, Balmes J, Tager IB. Association between lifetime ambient ozone exposure and pulmonary function in college freshmen—results of a pilot study. *Environ Res* 1997; 72: 8–23.

9 Tager IB, Balmes J, Lurmann F, Ngo L, Alcorn S, Kunzli N. Chronic exposure to ambient ozone and lung function in young adults. *Epidemiology* 2005; 16: 751–59.

10 Frischer T, Studnicka M, Gartner C, et al. Lung function growth and ambient ozone: a three-year population study in school children. *Am J Respir Crit Care Med* 1999; 160: 390–96.

11 Jedrychowski W, Flak E, Mroz E. The adverse effect of low levels of ambient air pollutants on lung function growth in preadolescent children. *Environ Health Perspect* 1999; 107: 669–74.

12 Horak FJ, Studnicka M, Gartner C, et al. Particulate matter and lung function growth in children: a 3-yr follow-up study in Austrian schoolchildren. *Eur Respir J* 2002; 19: 838–45.

13 Gauderman W, McConnell R, Gilliland F, et al. Association between air pollution and lung function growth in southern California children. *Am J Respir Crit Care Med* 2000; 162: 1383–90.

14 Gauderman W, Gilliland F, Vora H, et al. Association between air pollution and lung function growth in southern California children: results from a second cohort. *Am J Respir Crit Care Med* 2002; 166: 76–84.

15 Gauderman W, Avol E, Gilliland F, et al. The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 2004; 351: 1057–67.

16 Gauderman W, Avol E, Lurmann F, et al. Childhood asthma and exposure to traffic and nitrogen dioxide. *Epidemiology* 2005; 16: 737–43.

17 Nicolai T, Carr D, Weiland SK, et al. Urban traffic and pollutant exposure related to respiratory outcomes and atopy in a large sample of children. *Eur Respir J* 2003; 21: 956–63.

18 Venn A, Lewis S, Cooper M, et al. Local road traffic activity and the prevalence, severity, and persistence of wheeze in school children: combined cross sectional and longitudinal study. *Occup Environ Med* 2000; 57: 152–58.

19 Venn AJ, Lewis SA, Cooper M, Hubbard R, Britton J. Living near a main road and the risk of wheezing illness in children. *Am J Respir Crit Care Med* 2001; 164: 2177–80.

20 van Vliet P, Knape M, de Hartog J, Janssen N, Harssema H, Brunekreef B. Motor vehicle exhaust and chronic respiratory symptoms in children living near freeways. *Environ Res* 1997; 74: 122–32.

21 Hirsch T, Weiland SK, von Mutius E, et al. Inner city air pollution and respiratory health and atopy in children. *Eur Respir J* 1999; 14: 669–77.

22 Edwards J, Walters S, Griffiths RK. Hospital admissions for asthma in preschool children: relationship to major roads in Birmingham, United Kingdom. *Arch Environ Health* 1994; 49: 223–27.

23 Kim J, Smorodinsky S, Lipsett M, Singer BC, Hodgson AT, Ostro B. Traffic-related air pollution near busy roads: the East Bay Children's Respiratory Health Study. *Am J Respir Crit Care Med* 2004; 170: 520–26.

24 Brauer M, Hoek G, Van Vliet P, et al. Air pollution from traffic and the development of respiratory infections and asthmatic and allergic symptoms in children. *Am J Respir Crit Care Med* 2002; 166: 1092–98.

25 Zmirou D, Gauvin S, Pin I, et al. Traffic related air pollution and incidence of childhood asthma: results of the Vesta case-control study. *J Epidemiol Community Health* 2004; 58: 18–23.

26 Delfino RJ. Epidemiologic evidence for asthma and exposure to air toxics: linkages between occupational, indoor, and community air pollution research. *Environ Health Perspect* 2002; 110 (suppl 4): 573–89.

27 Janssen NA, Brunekreef B, van Vliet P, et al. The relationship between air pollution from heavy traffic and allergic sensitization, bronchial hyperresponsiveness, and respiratory symptoms in Dutch schoolchildren. *Environ Health Perspect* 2003; 111: 1512–18.

28 McConnell R, Berhane K, Yao L, et al. Traffic, susceptibility, and childhood asthma. *Env Health Perspect* 2006; 114: 766–72.

29 Brunekreef B, Janssen N, de Hartog J, Harssema H, Knape M, van Vliet P. Air pollution from truck traffic and lung function in children living near motorways. *Am J Epidemiol* 1997; 8: 298–303.

30 Wjst M, Reitmeir P, Dold S, et al. Road traffic and adverse effects on respiratory health in children. *BMJ* 1993; 307: 596–600.

31 Sugiri D, Ranft U, Schikowski T, Kramer U. The influence of large-scale airborne particle decline and traffic-related exposure on children's lung function. *Environ Health Perspect* 2006; 114: 282–88.

32 Kulkarni N, Pierse N, Rushton L, Grigg J. Carbon in airway macrophages and lung function in children. *N Engl J Med* 2006; 355: 21–30.

33 Hole D, Watt G, Davey Smith G, et al. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ* 1996; 313: 711–15.

34 Knuiman M, James A, Divitini M, et al. Lung function, respiratory symptoms, and mortality: results from the Busselton Health Study. *Ann Epidemiol* 1999; 9: 297–306.

35 Schunemann H, Dorn J, Grant B, et al. Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. *Chest* 2000; 118: 656–64.

36 Schroeder E, Welch V, Couper D, et al. Lung function and incident coronary heart disease, the Atherosclerosis Risk in Communities Study. *Am J Epidemiol* 2003; 158: 1171–81.

37 Friedman G, Klatsky A, Siegelaub A, et al. Lung function and risk of myocardial infarction and sudden cardiac death. *N Engl J Med* 1976; 294: 1071–75.

38 Kannell W, Hubert H, Lew E, Jones J. Vital capacity as a predictor of cardiovascular disease: the Framingham Study. *Am Heart J* 1983; 105: 311–15.

39 Ashley F, Kannell W, Sorlie P, et al. Pulmonary function: relation to aging, cigarette habit, and mortality. The Framingham Study. *Ann Intern Med* 1975; 82: 739–45.

40 Peters J, Avol E, Navidi W, et al. A study of twelve southern California communities with differing levels and types of air pollution I. Prevalence of respiratory morbidity. *Am J Respir Crit Care Med* 1999; 159: 760–67.

41 Benson P. CALINE4—A dispersion model for predicting air pollution concentrations near roadways. Sacramento: California Department of Transportation, 1989.

42 Berhane K, Gauderman W, Stram D, Thomas D. Statistical issues in studies of the long term effects of air pollution: the southern California Children's Health Study (with discussion). *Stat Sci* 2005; 19: 414–49.

GL14 Continued

41 Wang X, Dockery D, Wypij D, et al. Pulmonary function growth velocity in children 6 to 18 years of age. *Am Rev Respir Dis* 1993; 148: 1502–08.

44 Zhu Y, Hinds WC, Kim S, Sioutas C. Concentration and size distribution of ultrafine particles near a major highway. *J Air Waste Manag Assoc* 2002; 52: 1032–42.

45 Gilbert NL, Woodhouse S, Stieb DM, Brook JR. Ambient nitrogen dioxide and distance from a major highway. *Sci Total Environ* 2003; 312: 43–46.

46 Zhu Y, Kuhn T, Mayo P, Hinds WC. Comparison of daytime and nighttime concentration profiles and size distributions of ultrafine particles near a major highway. *Environ Sci Technol* 2006; 40: 2531–36.

47 Brauer M, Hoek G, van Vliet P, et al. Estimating long-term average particulate air pollution concentrations: application of traffic indicators and geographic information systems. *Epidemiology* 2003; 14: 228–39.

48 Gilbert NL, Goldberg MS, Beckerman B, Brook JR, Jerrett M. Assessing spatial variability of ambient nitrogen dioxide in Montreal, Canada, with a land-use regression model. *J Air Waste Manag Assoc* 2005; 55: 1059–63.

49 Gonzales M, Qualls C, Hudgens E, Neas L. Characterization of a spatial gradient of nitrogen dioxide across a United States-Mexico border city during winter. *Sci Total Environ* 2005; 337: 163–73.

50 Fischer PH, Hoek G, Van Reeuwijk H, et al. Traffic-related differences in outdoor and indoor concentrations of particles and volatile organic compounds in Amsterdam. *Atmos Environ* 2000; 34: 3713–22.

51 Zmirou-Knape MC, Janssen NAH, de Hartog JJ, Van Vliet PHN, Harssema JS, Brunekreef B. Air pollution from traffic in city districts near major motorways. *Atmos Environ* 1998; 32: 1921–30.

52 Khan A, Li J, Hussain L. Atmospheric transport of elemental carbon. *J Geophys Res* 2006; 111: D04303.

53 Manchester-Neesvig J, Schauer J, Cass G. The distribution of particle-phase organic compounds in the atmosphere and their use for source apportionment during the southern California Children's Health Study. *J Air Waste Manag Assoc* 2003; 53: 1065–79.

54 Li N, Hao M, Phalen RF, Hinds WC, Nel AE. Particulate air pollutants and asthma. A paradigm for the role of oxidative stress in PM-induced adverse health effects. *Clin Immunol* 2003; 109: 250–65.

55 Nel A. Atmosphere. Air pollution-related illness: effects of particles. *Science* 2005; 308: 804–06.

GL14 Continued

Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study

Correspondence to: Dr W James Gauderman jimg@usc.edu

	n	Mean number of FTFs	Children with 8-years' follow-up		Female (%)	Asthma (%)	Race/Ethnic origin (%)				
			n	(%)			Afr-Am	NW	AA	Asian	Other
Riverside	329	5·0	323	97·4	50·5	34·6	36·5	42·0	12·5	7·4	1·7
Atascadero	278	6·8	117	42·1	48·9	29·3	25·9	14·8	1·1	1·1	7·9
Alpine	308	6·2	321	99·1	50·1	32·9	25·0	28·5	0·0	0·3	5·8
Long Beach	370	6·1	141	44·1	47·5	13·9	32·2	24·7	18·4	25·3	9·4
San Dimas	293	6·4	317	99·9	50·2	35·3	30·7	32·4	3·1	0·7	3·1
Santa Maria	319	5·7	100	30·1	45·4	14·6	25·7	60·9	1·0	4·5	6·5
Lake Elsinore	305	6·0	104	34·0	50·0	12·5	64·5	25·8	2·3	2·0	3·5
Mira Loma	319	5·9	318	37·0	50·2	12·3	51·7	47·3	1·6	0·9	3·5
Upland	283	6·9	150	53·0	51·7	14·7	66·4	17·3	4·3	8·5	3·5
Lancaster	315	5·5	110	34·9	52·1	14·7	50·4	29·8	9·2	2·2	6·7
Lompoc	281	6·3	113	40·2	47·0	10·3	55·2	26·1	5·7	5·3	5·7
Lake Arrowhead	335	6·2	331	98·1	51·3	14·6	73·1	20·0	0·3	0·9	5·7
Overall	3677	6·2	3445	93·3	49·9	14·3	54·5	30·2	5·6	4·4	5·0

NHW=Non-Hispanic white; NHB=Non-Hispanic black; AA=African American; FTF=full-time facilities.

Webtable 1: Participants' characteristics by community

GL14 Continued

Webtable

Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study

	n	Residential distance to freeway					Major non-freeway road (m)				Model-based pollution from freeways (quartile*)				Major non-freeway roads (quartile*)			
		<500	500–1000	1000–1500	>1500	<75	75–150	150–300	>300	4th	3rd	2nd	1st	4th	3rd	2nd	1st
Riverside	349	103	66	61	99	46	45	90	168	193	123	14	2	146	138	41	1
Atascadero	278	81	60	46	89	11	8	35	244	9	70	155	53	4	17	58	189
Alpine	308	81	54	47	131	41	9	31	227	15	135	141	18	21	43	73	171
Long Beach	329	54	64	54	148	55	79	78	108	264	54	2	0	331	9	0	0
San Dimas	293	47	145	83	18	46	47	62	138	282	8	1	2	169	114	9	1
Santa Maria	310	44	24	58	184	25	47	104	134	0	7	73	230	18	191	64	37
Lake Elsinore	305	22	17	7	259	30	33	56	186	1	41	184	80	17	77	103	159
Mira Loma	319	9	30	45	235	20	37	57	205	11	304	2	2	12	43	212	52
Upland	283	4	6	6	279	53	57	67	115	4	2	85	192	83	100	60	40
Lancaster	315	3	35	31	246	52	24	91	148	0	21	168	186	48	127	128	12
Compton	281	0	0	0	281	5	21	33	222	..	..	..	..	4	26	88	163
Lake Arrowhead	335	0	0	0	335	0	0	0	335	..	..	..	..	..	..	..	..
Total	3677	449	545	420	2305	385	407	673	1217	766	795	765	765	836	835	836	835

*Tertile is for major freeway (other Compton or Lake Arrowhead, and for major non-freeway road (other Lake Arrowhead).

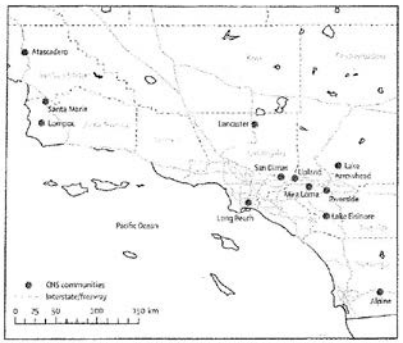
Webtable 2: Number of study participants with in categories of four traffic indicators

Correspondence to:
Dr W James Gauderman
jimg@usc.edu

GL14 Continued

Webfigure

Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study



Webfigure: Location of the 12 Children's Health Study communities and the major freeways (purple lines) in southern California.

Correspondence to:
Dr W James Gauderman
jimg@usc.edu

GL14 Continued

Webappendix

Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study

Correspondence to:
Dr W James Gauderman
jimg@usc.edu

Details of exposure assessment

Traffic exposures were assigned to each child on the basis of the residence at study entry. Residence addresses were standardised and their locations geocoded by use of the TeleAtlas database and software (Tele Atlas Inc., Menlo Park, CA, www.na.teleatlas.com). We used ERSI ArcGIS version 8.3 (ESRI, Redland, CA www.esri.com) software to calculate the distance from each residence to the nearest freeway, defined as an interstate freeway, US highway, or restricted-access highway, and to the nearest major non-freeway road, which included other types of highways and large roads. Yearly average daily traffic volumes were obtained from the California Department of Transportation Highway Performance Monitoring System for the year 2000. To obtain model-based estimates of traffic-related pollution exposure, we used the CALINE4 line-source air-quality dispersion model, separately for freeways and non-freeway roads.[1] The main model inputs included roadway geometry, traffic volumes, meteorological conditions (wind speed and direction, atmospheric stability, and mixing heights), and vehicle emission rates. We used the CALINE4 model to predict nitrogen dioxide concentrations derived from freeways and non-freeways at each child's home. Categories of exposure were then formed on the basis of quartiles of the within-community distribution of child-specific predictions, specifically based on cutpoints 0·6, 1·9, and 7·1 parts per billion (ppb) from freeways, and 1·5, 2·6, and 5·3 ppb from non-freeway roads. We also used the CALINE4 model to predict concentrations of other traffic-related pollutants, including oxides of nitrogen, elemental carbon, and carbon monoxide. However, predictions for each of these pollutants were almost perfectly correlated (around 0·99) with predictions of nitrogen dioxide. Thus, our model-based concentrations should be viewed as general measures of traffic-related pollution rather than this pollutant specifically. For both distance and model-based traffic indicators, within-community deviations from the corresponding community mean of the indicator were used in the health models to assess local (rather than between-community) effects.

Air-pollution monitoring stations were established in each of the 12 study communities and provided continuous monitoring data from 1994 to 2003. Each station measured average hourly concentrations of ozone, nitrogen dioxide, and particulate matter with aerodynamic diameter less than 10 μm (PM_{10}). Stations also collected 2-week integrated filter samples for measuring acid vapour and $PM_{2.5}$ mass and chemistry. Acid vapour included both inorganic (nitric, hydrochloric) and organic (formic, acetic) acids. For statistical analysis, we used total acid calculated as the sum of nitric, formic, and acetic acid concentrations. Hydrochloric acid was excluded from this sum, because concentrations were very low and close to the detection limit. In addition to measurement of $PM_{2.5}$ mass, we measured concentrations of elemental carbon and organic carbon, using the NIOSH 5040 method.[2] We calculated yearly averages on the basis of 24 h (PM_{10}, nitrogen dioxide) or 2-week ($PM_{2.5}$, elemental carbon, organic carbon, acid) average concentrations. For ozone, we calculated the yearly average of the 1000–1800 h (8 h daytime) average. Long-term mean pollutant concentrations (between 1994 and 2000 for cohort 1 and 1996 and 2003 for cohort 2) were also calculated for use in the statistical analysis of the lung-function outcomes. The distribution and correlation structure of these pollutants across communities, and their effect on lung function development, have been previously reported.[3–5] In this paper, we used community-average pollutant concentrations in models of local traffic exposure to investigate their combined effects and to explore the possibility that traffic effects vary according to regional air quality.

References

1 Benson P. CALINE4—A dispersion model for predicting air pollution concentrations near roadways. Sacramento: California Department of Transportation, 1989.

2 NIOSH Method 5040 Issue 3 (interim): Elemental Carbon (Diesel Exhaust). In NIOSH Manual of Analytical Methods. Cincinnati, Ohio: National Institute of Occupational Safety and Health, 1999.

3 Gauderman W, McConnell R, Gilliland F, et al. Association between air pollution and lung function growth in southern California children. *Am J Respir Crit Care Med* 2000; 162: 1383–90.

4 Gauderman W, Gilliland F, Vora H, et al. Association between air pollution and lung function growth in southern California children: results from a second cohort. *Am J Respir Crit Care Med* 2002; 166: 76–84.

5 Gauderman W, Avol E, Gilliland F, et al. The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 2004; 351: 1057–67

GL14 Continued

This page intentionally left blank.

GL15

City of Seal Beach

CITY HALL · 211 EIGHTH STREET
SEAL BEACH, CALIFORNIA 90740
(562) 431-2527 · www.sealbeachca.gov

RECEIVED
CEO OFFICE

JUL 18 2012

C. Byrne Jim B
Rose C. Niall B
Lance
File

July 16, 2012

Orange County Transportation Authority
c/o Paul Glaab, Chair, Board of Directors
550 S. Main Street
Orange, CA 92863-1584

Subject: I-405 Widening Project

Dear Chairperson Glaab:

The City of Seal Beach recognizes the fact that Orange County has a world class network of infrastructure and freeways. The quality of this system is responsible in large part by the voter's approval of Measure M and the Orange County Transportation Authority's ability to successfully manage this program. The I-405 Freeway is a concern of the voter's and is in need of improvement. It is extremely difficult to manage the Measure M program and in particular this I-405 Improvement project with competing interests and concerns from every agency and resident.

The City of Seal Beach does have concerns over the project. Seal Beach appreciates the efforts that OCTA has made to work with our staff and residents regarding concerns over the alternatives listed in the Environmental Impact Report/Environmental Impact Statement (EIR/EIS). Solutions to alleviate those concerns have to this point not been reached and the City of Seal Beach is compelled to communicate with OCTA prior to the closure of the comment period of the EIR/EIS document. 1

The main concerns expressed by residents of Seal Beach are:

1. Retention of existing College Park East sound wall in the current location;
2. Possible relocation of 2 gas/petroleum pipelines through College Park East;
3. Creation of a toll road (Alternative 3);
4. Increased traffic congestion along the I-405 freeway, including northbound bottlenecks resulting from required lanes merging before the LA County line;
5. Air quality and public health concerns

In August of 2009 the Notice of Intent/Notice of Preparation (NOI/NOP) was issued announcing commencement of the project. Seal Beach has been actively participating in the project having representation on both the Technical Advisory Committee and the Policy Advisory Committee throughout the Major Investment Study phase. The NOI/NOP stated that four "build" alternatives would be considered in the EIR/EIS. As indicated therein, within the confines of available Measure M/M2 funding, Alternative 4: Localized Improvements would provide an additional General Purpose (GP) lane at various locations and improve certain interchanges. In addition, the NOP/NOI and accompanying scoping notices stated that a "Transportation Systems Management/Transportation Demand Management/Mass Transit (TSM/TDM/Mass Transit) Alternative" would be examined in the EIR/EIS. That additional alternative would involve low-cost operational improvements rather than major capital projects and include auxiliary lanes, ramp metering, ridesharing, and traffic signal timing optimization. 2

GL15 Continued

Orange County Transportation Authority
Page Two
July 16, 2012

Those two notices announced alternatives are not adequately examined in the EIR/EIS. Without these alternatives, the project's "stakeholders" are deprived the opportunity to review the environmental impact and submit comments under the California Environmental Quality Act (CEQA) and National Environmental Protection Act (NEPA). In lieu of the presentation of a reasonable range of alternatives designed to foster public dialogue and discourse, the EIR/EIS is limited to a discussion of only three "build" alternatives comprising nothing more than minor variations to what amounts as the same project. A substantially broader array of possible alternatives, design variations, and operational changes are not considered. As such, for those and other reasons (e.g., lack of effective mitigation), the current EIR/EIS is inadequate and fails to comply the statutory intent and purpose. 2

By examining only a short segment of the freeway and ignoring the consequences of those adverse conditions, substantive issues affecting Seal Beach are all but ignored. Among its purposes, CEQA and NEPA are intended to foster informed decision making. Agencies are not mandated to take the most environmentally sensitive course of action but are required to first be fully informed about the choices they elect to make. The deficiencies of the existing EIR/EIS are so substantial as to prevent the City from understanding the consequences of the three "build" alternatives on both the natural and human environment, ensuring its constituents that the project's impacts are effectively mitigated, and allowing the City to support one course of action over another. The EIR/EIS document needs to be revised technically with the required additional alternatives and analysis to be a legally adequate assessment. 3

The City of Seal Beach appreciates working with OCTA and Caltrans regarding the concerns over this project, and requests that the partnership continue. Seal Beach's concerns as detailed within this letter will not be resolved without the continued effort to partner on the project.

Declaration of a formal position by the City of Seal Beach is premature and remains dependent upon the completion of an adequate environmental review. In order to preserve its legal remedies, however, the City of Seal Beach will formally respond to Caltrans before July 17, 2012. Despite this inadequacy, as Mayor, I am writing on behalf of the City Council and Seal Beach to oppose Alternatives 2 and 3. Seal Beach takes very seriously these concerns and is considering all options towards having those concerns addressed including outright opposition to the project. 4

If there are any questions please call 562.431.2527 ext. 1300.

Sincerely,

Michael Levitt
Mayor
City of Seal Beach

cc: OCTA Board
Will Kempton, CEO
California State Senator Tom Harman
California State Senator Lou Correa
California State Assembly Jose Solario
California State Assembly Jim Silva

GL16

City of Westminster

8200 Westminster Boulevard, Westminster, CA 92683 714.898.3311
www.westminster-ca.gov

MARGIE L. RICE
Mayor

TRI TA
Mayor Pro Tem

FRANK G. FRY
Council Member

ANDY QUACH
Council Member

TYLER DIEP
Council Member

J. MITCHELL WALLER
City Manager

Thursday, July 12, 2012

Smita Deshpande
Branch Chief - Caltrans District 12
2201 Dupont Drive, Suite 200
Irvine, CA 92612

RE: City of Westminster's Comments to Draft I-405 Improvement Project Environmental Impact Statement/Environmental Impact Report (EIS/EIR)

Dear Ms. Deshpande:

On behalf of the Westminster City Council, I would like to present you with comments to the Draft I-405 Improvement Project EIS/EIR.

We appreciate your effort in the I-405 Improvement Project and need your assistance in mitigating potential impacts to residents and businesses in our City. Please receive these comments to the Draft EIS/EIR. Take note that it is our goal to preserve quality of life for our residents and continue to promote a business-friendly environment during and after the construction of the project. Since the release of the Draft EIS/EIR, we have been in contact with OCTA in an effort to mitigate major areas of concern in our City. We would like the following to be entered into public record as formal comments to the Draft EIS/EIR:

Comment 1 - Westminster/Springdale Bridge Crossings

Impact: The proposed bridge reconstruction at this location has created grade differentials that require that ramps be installed to facilitate the transition from street elevation to private property elevation. This will impact the on-site parking and traffic circulation.

Mitigation: Work with city staff to revise on-site circulation for more effective traffic flow. Consider relocating the Springdale Avenue driveway to align with the new signalized Springdale Avenue Off-Ramp for improved site access.

1

Comment 2 - Goldenwest/Bolsa Bridge Crossings

Impact: The proposed bridge reconstruction at this location has resulted in the redesign of the northbound Goldenwest Street approach at Bolsa Avenue; a dedicated right-turn lane is proposed and necessary to maintain acceptable traffic signal operations and satisfy forecast traffic demand.

Mitigation: Work with city staff to revise the roadway alignment for Goldenwest Street at Bolsa Avenue. The proposed intersection capacity improvement is impactful to the City of Westminster only. A loss of

2

GL16 Continued

private property and city right-of-way is proposed for the east side of Goldenwest Street. For example at this location, the current design would impact 35 parking spaces, a sidewalk and a parkway, all in the City of Westminster, with zero property impacts on the west side of the street in Huntington Beach right-of-way. We request that the design team take a more balanced approach to right-of-way acquisition between the Cities of Westminster and Huntington Beach.

2

Comment 3 - Vacate Land to the City

The City would like surplus property, not used for the project and deemed unusable by the State, to be vacated to the City to enhance areas impacted by the project. For example, the reconstruction of the southbound I-405 on-ramp (east of Goldenwest Street) will result in an unused section of land immediately behind the commercial development at 15042 Goldenwest Street. This commercial development is regularly parked over capacity due to the successful businesses on site (El Torito and IHOP restaurants, retail commercial, etc.). Vacating the excess land would facilitate a parking lot expansion that would benefit the businesses and the City.

3

Comment 4 - Interstate 405 Southbound On/Off-Ramp at Westminster Mall Road

The south leg of the subject intersection connects the I-405 ramp and Westminster Mall Road to Bolsa Avenue. The local connector is a one-way street without ADA compliant pedestrian facilities. It has the potential to provide congestion relief to the intersection of Goldenwest Street and Bolsa Avenue. We ask that the design team work with city staff to improve the connector as an access to Bolsa Avenue from the freeway and enhance pedestrian safety.

4

Comment 5 - Bolsa Avenue West of Goldenwest Street

Impact: The proposed bridge reconstruction at this location requires that the vertical elevation transitions be extended further than they are today. The transition to the west of the Bolsa Bridge, per the Draft EIR, would result in the removal of 20 parking spaces at 100 Westminster Mall (Sears Auto Center).

Mitigation: Work with city staff to revise the roadway alignment on Bolsa Avenue west of Goldenwest Street. We request that the design team take a more balanced approach to right-of-way acquisition and consider all possible methods of limiting property impacts. These methods include, but are not limited to, roadway realignment, reduced width travel lanes, etc.

5

Comment 6 - Sound Wall Installation and Replacement

The City requests that a more balanced and fair approach to sound wall installation and replacement be considered by the design team. The current sound wall section of the Draft EIS/EIR does not accurately address the issue of aging sound walls that are in need of repair and/or sound walls that were not property constructed in the first place. It presents very strict and unrealistic criteria for implementing sound mitigation. We ask that additional analysis be performed during the design phase of the project that considers other sound wall installation measures outside the current criteria. For example, sound walls that were not properly constructed need to be reconstructed to the latest standards. Sound wall concerns that have previously been reported to Caltrans must be revisited as part of this project and be considered for reconstruction on a case by case basis.

6

The project team (OCTA, Caltrans and Parsons) have been very helpful and accommodating to the City of Westminster. However, overcoming the challenges as outlined in the aforementioned comments will require even more collaboration. We support the I-405 Improvement Project as outlined in the

7

GL16 Continued

Renewed Measure M; the project will improve the I-405 freeway for the benefit of County. However, the Westminster City Council and I take the concerns listed in this letter very seriously. We reserve the right to mitigate unknown issues that may arise after the inception of the "design-build" phase of the project implementation. The City will consider all build options, with the exception of Alternative 3. This option is unacceptable to Westminster residents, and will create a toll/express facility that will restrict access to our business community. **7**

Respectfully Yours,

Margie L. Rice

MARGIE L. RICE
MAYOR

RESPONSE TO GOVERNMENT (LOCAL) COMMENTS (GL)

Response to Comment Letter GL1

Comment GL1-1

Caltrans and OCTA thank the City of Costa Mesa for participating in the environmental process for the I-405 Improvement Project. The City's comments were considered during identification of the Preferred Alternative as described in the Final EIR/EIS. The City will be notified when the Final EIR/EIS is available for review.

Your comment letter contained many exhibits, including a letter from Mayor Bever to Paul Glaab. That letter contains information in summary form more fully elucidated in your comment letter. Consequently, that letter has not received separate responses.

Your comment letter also contained many e-mails from residents. All of those e-mails were sent prior to circulation of the Draft EIR/EIS and consequently cannot be comments on the Draft EIR/EIS. Consequently, those e-mails have not been responded to.

The Draft EIR/EIS and this Final EIR/EIS were prepared by Caltrans and OCTA's consultant. Caltrans has a multilevel rigorous independent review process that is completed independently at the District and Headquarters Levels. Additionally, the document has been through an independent legal review prior to releasing the Draft EIR/EIS and has gone through a legal sufficiency review prior to certifying the Final EIR/EIS. Detailed requirements of the independent review process are provided on the Caltrans SER Web site, which is continually updated to reflect changes in environmental regulations and/or Caltrans policies. Caltrans maintains records of their compliance with the 5-step review, which documents the independent review by technical specialists and senior environmental planners, headquarters staff, and Caltrans Legal.

As disclosed in Section 3.2.6.3 of the Draft EIR/EIS, at the time the Draft EIR/EIS was circulated to the public, the project description in the RTP/FTIP included a design concept and scope for Alternative 1; however, the design concept and scope for Alternatives 2 and 3, as described in Chapter 2, were substantially different from what was analyzed in the 2008 RTP. OCTA, not Caltrans, initiated the change in the project description shown in Attachment A of the comment letter. All alternatives were represented equally in the Draft EIR/EIS, and there is no proclivity toward any of the build alternatives. Alternatives 2 and 3 are required to go through the SCAG RTP and FTIP amendment process prior to being able to determine consistency with the plans; however, the regional operational emissions analysis was completed for all alternatives

and would be less than the no-build conditions in years 2020 and 2040. The amendment process is required to be completed prior to approval of the Final EIR/EIS. The Preferred Alternative identified in the Final EIR/EIS is consistent with the description in the 2012 RTP and FTIP.

Comment GL1-2

The Draft EIR/EIS, including specialized technical studies (all technical studies are available for review on the Caltrans D12 Web site at http://www.dot.ca.gov/dist12/405/index.htm#Technical), represents a comprehensive analysis of the reasonably foreseeable environmental effects of the proposed build alternatives on the Human (Section 3.1), Physical (Section 3.2), and Biological (Section 3.3) environments. Where applicable, the Final EIR/EIS has been revised/updated to clarify/correct information based on the public comments received on the Draft EIR/EIS. As described in the Draft EIR/EIS, only Alternative 3 would require demolition/reconstruction of the Fairview Road Overcrossing and Harbor Boulevard southbound loop on-ramp. Should Alternative 3 be identified as the Preferred Alternative, Caltrans/OCTA will continue to work with the City to minimize project effects on the City and its residents.

Please also see Common Response –Preferred Alternative Identification.

Construction Impacts: Construction impacts are discussed in detail, based on the preliminary engineering and analysis for all of the build alternatives. Construction impacts are discussed for all of the build alternatives in every section, as applicable, within the environmental consequences subsection as temporary impacts. Caltrans and OCTA have evaluated options to minimize project effects from Alternative 3 on the City, including revised project geometrics to avoid reconstruction of the Fairview Road Overcrossing or truncating the project to modify the southern project limits to begin north of Fairview Road. Project construction impacts are typical of large construction projects, and other than those impacts that were identified as significant in Chapter 4 of the Draft and Final EIR/EIS, no other significant impacts were identified.

Ramp Closures: A ramp closure study was prepared for the project in accordance with the Caltrans Project Development Procedures Manual and was provided in "Appendix C Ramp Closure Study" of the Community Impact Assessment. Proposed detour routes associated with the long-term ramp closures (i.e., ramps closed at least 10 consecutive days) were provided in the Draft EIR/EIS Appendix M, Proposed Ramp Closure Detour Routes. Caltrans and OCTA will continue to work with all affected cities to minimize construction closures/impacts on special events and venues, including the OC Fair & Event Center. Although the contractor may not be working during holidays, it is not likely that all ramps within the corridor will be available during the holiday seasons. Caltrans and OCTA will continue to work with the City to minimize/coordinate closure of ramps during the holiday seasons.